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DEPARTMENT OF HEALTH AND HUMAN SERVICES 43

Food and Drug Administration

21 CFR Parts 16 and 99

[Docket No. 98N–0222]

RIN 0910–AB23

Dissemination of Information on Unapproved/New Uses for Marketed Drugs, Biologics, and Devices

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is issuing final regulations pertaining to the dissemination of information on unapproved uses (also referred to as ''new uses'' and ''off-label uses'') for marketed drugs, including biologics, and devices. The final rule describes the new use information that a manufacturer may disseminate and describes the content of and establishes procedures for a manufacturer's submission to FDA before it may begin disseminating information on the new use. The final rule also describes how manufacturers seeking to disseminate information on a new use must agree to submit a supplemental application for that use within a specified period of time, unless a supplemental application already has been submitted or FDA has exempted the manufacturer from the requirement to submit a supplement. The final rule provides for requests to extend the time period for submitting a supplemental application for a new use and describes how a manufacturer can seek an exemption from the requirement to submit a supplemental application for the new use. Additionally, the final rule discusses FDA actions in response to manufacturers' submissions, corrective actions that FDA may take or require, and recordkeeping and reporting requirements. The final rule implements sections 551 through 557

of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 360aaa through 360aaa-6) as amended by section 401 of the Food and Drug Administration Modernization Act of 1997 (FDAMA).

DATES: The final rule is effective (*insert date of publication in the* **Federal Register**.) Written comments on the information collection requirements should be submitted by (*insert date 60 days after date of publication in the* **Federal Register**.)

ADDRESSES: Submit written comments on the information collection requirements to the Dockets Management Branch (HFA–305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

FOR FURTHER INFORMATION CONTACT:

Regarding biological products and devices regulated by the Center for Biologics Evaluation and Research: Toni M. Stifano, Center for Biologics Evaluation and Research (HFM–602), Food and Drug Administration, 1401 Rockville Pike, Rockville, MD 20852, 301–827–3028;

Regarding human drug products: Laurie B. Burke, Center for Drug Evaluation and Research (HFD–40), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301–827–2828;

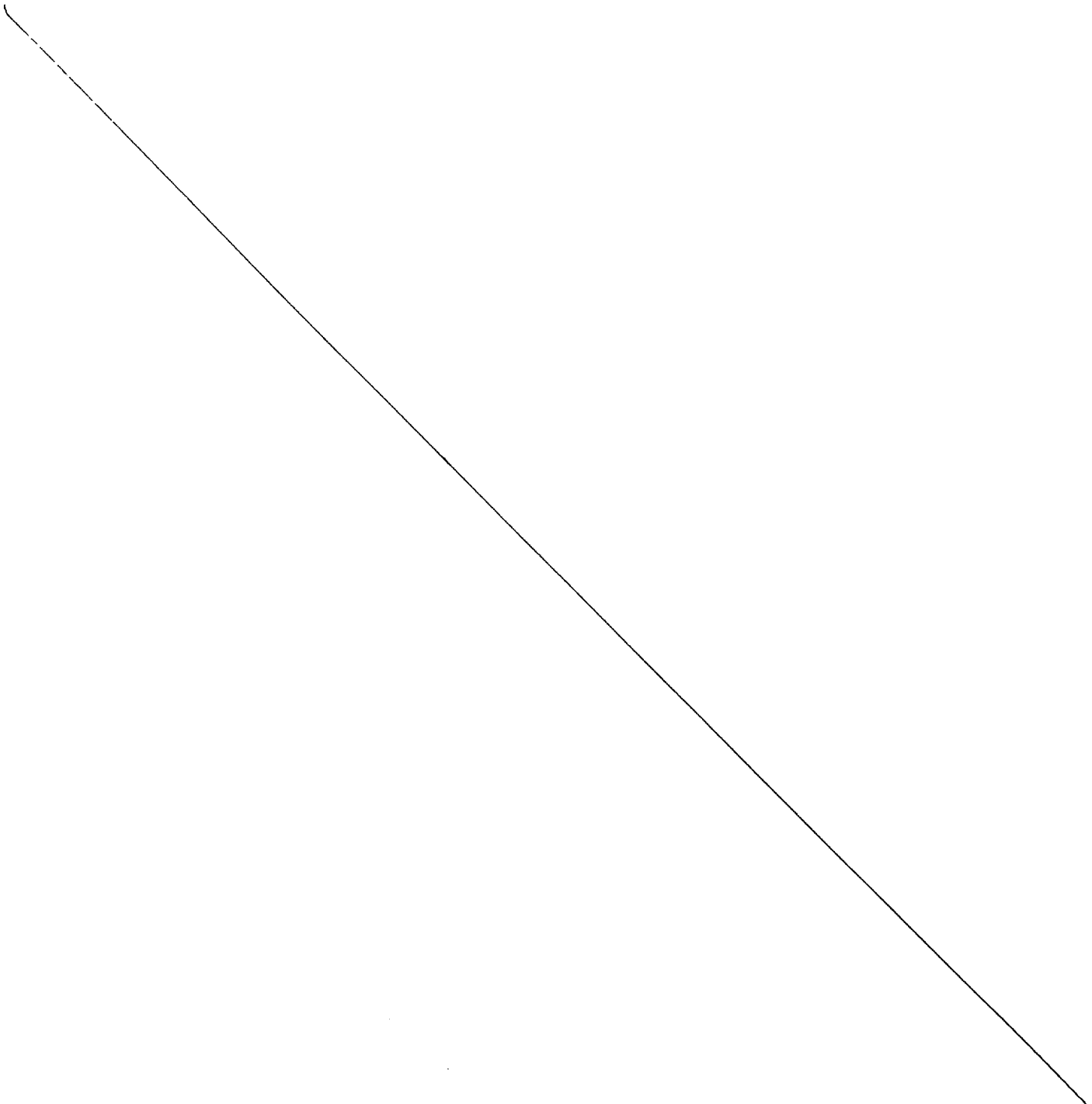
Regarding medical devices: Byron L. Tart, Center for Devices and Radiological Health (HFZ–302), Food and Drug Administration, 2098 Gaither Rd., Rockville, MD 20850, 301–594–4639.

SUPPLEMENTARY INFORMATION:

I. Introduction

In the **Federal Register** of June 8, 1998 (63 FR 31143), FDA published a proposed rule that would add to title 21 of the Code of Federal Regulations (CFR) a new part 99 entitled, ''Dissemination of Information on Unapproved/New Uses for Marketed Drugs, Biologics, and Devices.''

The proposed rule was intended to implement section 401 of FDAMA. In brief, section 401 of FDAMA amended the act to permit drug, biologic, and device manufacturers to disseminate certain written information concerning the safety, effectiveness, or benefits of a use that is not described in the product's approved labeling to health care practitioners, pharmacy benefit managers, health insurance issuers, group health plans, and Federal and State Government agencies, provided that the manufacturer complies with certain statutory requirements. For example, the



information that is to be disseminated must be about a drug or device that is being legally marketed; it must be in the form of an unabridged reprint or copy of a peer-reviewed journal article or reference publication; and it must not be derived from another manufacturer's clinical research, unless that other manufacturer has given its permission for the dissemination. The information must be accompanied by certain information, including a prominently displayed statement that the information discusses a use or uses that have not been approved or cleared by FDA. Additionally, 60 days prior to the dissemination, the manufacturer must submit to FDA a copy of the information to be disseminated and any other clinical trial information that the manufacturer has relating to the safety or effectiveness of the new use, any reports of clinical experience that pertain to the safety of the new use, and a summary of such information.

A detailed description of section 401 of FDAMA appeared in the preamble to the proposed rule (see 63 FR 31143 at 31144 and 31145).

II. Highlights of the Final Rule

Although the statute is very detailed, and the final rule closely tracks its provisions, there are some places where the regulation fills in the details of the statutory requirements. For example, the final rule defines terms that were not defined in the legislation (e.g., ''supplemental application'' and ''clinical investigation,'' and it explains concepts that required additional explanation (e.g., what is meant by the term ''unabridged''). The final rule also sets forth the more detailed procedures for how to submit the required information to FDA before disseminating any new use information (e.g., where the information should be submitted and how many copies are required). Finally, the final rule defines what is meant by the basic criteria that the statute sets forth for granting an exemption from the requirement to submit a supplement application on the basis that it would be unethical or economically prohibitive to conduct the studies needed to submit a supplemental application.

The final rule has been revised in response to comments received on the proposal. For example, § 99.3 was revised to add a definition for pharmacy benefit manger, which is not included

in the statute. The definition of ''clinical investigation'' in § 99.3 also was revised. Section 99.101 was revised to reflect FDA's position that most journal articles and reference texts (as those terms are defined in the regulation) would be considered to be scientifically sound and to describe specific instances (e.g., letters to the editor, Phase 1 trials in healthy individuals) when that would not be the case.

Section 99.103 revised the mandatory statement that the disseminated information has not been approved or cleared by FDA. That section also was revised to ensure that the financial disclosures required under this part would be consistent with FDA's final rule on financial disclosures by clinical investigators.

Sections 99.201(a)(4)(i)(B) and (a)(4)(ii)(B), 99.203(b), and 99.401(b) were revised to clarify that for purposes of computing time periods that begin on the date of initial dissemination, FDA will look to the date that dissemination can begin. This clarification was necessary because FDA will not know when a manufacturer actually begins to disseminate materials.

Sections 99.203 and 99.303 were revised to clarify that there are two different ways that FDA can extend the time period for completing the studies needed to submit a supplemental application for a new use: One before any studies have begun and one after the studies have begun. FDA also revised the standard for granting an exemption from the requirement to submit a supplemental application on the basis that it would be economically prohibitive. The focus is now on the revenue from the new use rather than the revenue from the product.

In § 99.301, FDA clarified when it would require a manufacturer to keep records identifying the individual recipients of new use information as opposed to just the categories of such recipients. Finally, the final rule was revised to ensure that a decision on a new use submission would be made within 60 days.

III. Responses to Comments on the Proposed Rule

FDA received over 50 written comments on the proposed rule. In addition, on July 8, 1998, FDA held a public meeting on the proposed rule. Thirteen speakers commented on the proposal.

In general, the comments expressed a diverse range of opinions, both favoring and opposing the proposed rule, and were submitted by health professionals, medical organizations, consumer groups, patient groups, a medical journal, members of Congress, trade associations, and manufacturers.

A. General Comments

Several comments addressed the concept of disseminating information on unapproved or new uses rather than the proposed rule itself. Other comments sought further restrictions on the dissemination of information on unapproved or new uses, while still other comments sought to expand the rule to cover more products.

1. A number of comments expressed concern that the proposed rule could result in harm to patients. One comment expressed concern over the self-policing aspects of the rule. Another comment cited several examples where drugs were administered for unapproved uses and proved to be harmful. The comment stated that dissemination of information on unapproved uses for approved drugs would further encourage the use of ''untested'' drugs and discourage clinical trials that would show whether the drugs are safe and effective for their intended uses. The comment asked FDA to ''revise or abandon these regulations so as to continue to protect consumers from untested and potentially dangerous drugs.'' One comment argued that the new rule was not ''warranted'' because the disseminated information may be inappropriate and would pose a significant risk to public health. The comment further argued that current practices in this area are the best way to handle information on unapproved uses. Finally, a number of comments expressed concern that FDA does not have sufficient resources to implement the regulation in a manner that can adequately protect the public health. Such comments urged FDA to direct adequate resources to implementation.

Section 401(c) of FDAMA required FDA to issue regulations to implement sections 551 through 557 of the act by November 21, 1998. The final rule, which closely tracks the statutory language, represents FDA's effort to comply with that requirement. FDA is committed to implementing this new statutory authority consistent with its obligation to protect the public health.

2. Several comments claimed that dissemination of information on unapproved or new uses of drugs for which pediatric labeling is not available would be contrary to section 505A of the act (21 U.S.C. 355A) as it pertains to pediatric studies of drugs because it would impede the development of pediatric data. Several comments said that dissemination of information on unapproved uses for pediatric therapy should be limited to drugs that have ''sufficient labeling in the ages of the children addressed by the information disseminated.'' Another comment noted that dissemination of information for an unapproved use of a drug in children when the drug's approved use has not been tested for safety in pediatric patients may pose even more risk than unapproved uses generally. Others said that for drugs without labeling for pediatric populations or specific age populations, drug manufacturers should not be able to disseminate unapproved use information about pediatric populations or about specific age populations not specified in the label, unless such information is specifically requested by the physician.

FDA declines to amend the rule as suggested by the comments. It is FDA's hope that the statutory scheme set forth in section 401 of FDAMA and implemented by this part will actually stimulate research and the development of data on new uses, including pediatric uses. Moreover, nothing in section 401 of FDAMA or its legislative history suggests that Congress intended to exclude pediatric uses from section 551 of the act or to further limit how information on such uses can be disseminated. Finally, the act does not require that the disseminated information be specifically requested by a physician in order to be disseminated.

Although FDA is not amending the codified language in any way, it does recognize that the potential dangers of unapproved uses in children may be greater than for adults because few drugs have been tested in children. The agency will take this into account in making a determination as to whether a proposed dissemination of information on a new use poses a significant risk to public health such that the dissemination under this part should not be permitted.

3. One comment would revise the rule to exclude drugs that may be covered by orphan drug exclusivity. The comment explained that a manufacturer may obtain orphan drug exclusivity for

a particular use of a drug, but that other manufacturers could be marketing the same drug for non-orphan indications. The comment stated that such other manufacturers could disseminate information on the orphan indication, thereby undermining the value of orphan drug exclusivity.

There is no indication in section 401 of FDAMA or its legislative history that Congress intended the dissemination of information on unapproved uses of drugs and devices to undermine patent protection or exclusivity granted to a product under the Orphan Drug Act, the Waxman-Hatch Amendments, or the pediatric exclusivity provisions in section 111 of FDAMA. Therefore, an indication that is not included in a particular sponsor's approved product labeling because the indication is protected by patent or exclusivity is not eligible for dissemination under part 99.

4. Several comments urged FDA to broaden the proposal to include over-the-counter (OTC) drug products being marketed under an OTC monograph.

Section 401 of FDAMA requires that in the case of a drug, there be in effect for the drug an application filed under section 505(b) or (j) of the act. OTC drugs being marketed under an OTC monograph do not have an application filed under section 505(b) or (j) of the act in effect. Therefore, FDA declines to revise the rule as suggested in these comments.

5. One comment stated that companies sometimes assist physicians and patients in obtaining reimbursement from Medicare, Medicaid, and private insurers by furnishing copies of journal articles and reference publications on unapproved uses to the insurer or government agency when reimbursement is denied on the ground that use of the product is experimental. The comment concluded that this practice appeared to be legal prior to the passage of section 401 of FDAMA and asked FDA to clarify that it did not become illegal as a result of FDAMA.

Prior to passage of FDAMA, the practice described in this comment was not permissible unless the unapproved use information was provided in response to an unsolicited request for such information. FDA's policy, which allows manufacturers to provide unapproved use information in response to an unsolicited request, was not affected by FDAMA (see section 557(a) of the act). Accordingly, manufacturers who wish to furnish unapproved use information as described

in the comment may do so if it is in response to an unsolicited request. Otherwise, they must comply with the requirements set forth in section 401 of FDAMA and this part.

6. One comment asserted that the proposal should recognize the specific legal authorization for manufacturers to provide off-label information to health care practitioners in response to an unsolicited request.

Section 401 of FDAMA added a new section 557(a) of the act, which provides that nothing in section 551 of the act shall be construed as prohibiting a manufacturer from disseminating information in response to an unsolicited request from a health care practitioner. Although FDA does not construe section 557(a) of the act as a specific legal authorization for manufacturers to provide off-label use information to health care practitioners in response to an unsolicited request, § 99.1(b) of the final rule recognizes this statutory provision.

7. One comment stated that FDA should exempt manufacturers from the ''pre-approval and reporting requirements'' when the primary focus of a publication is on the approved uses of the product.

Section 401 of FDAMA and this part do not cover publications regarding approved uses. FDA intends to permit manufacturers to disseminate certain information that focuses primarily on approved uses and that report the results of studies that have been relied on by FDA in its approval or clearance of a drug or device without meeting all of the requirements set forth in this part. (Cf. Guidance to Industry on Dissemination of Reprints of Certain Published Original Data (61 FR 52800, October 8, 1996). The agency was enjoined from applying this guidance document in *Washington Legal Foundation* v. *Friedman*, CA No. 1:94CV1306 (D.D.C. July 30, 1998) (hereinafter referred to as *WLF* v. *Friedman*). FDA sought clarification on the scope of the order through a motion to amend the judgment in that case.) FDA plans to issue guidance on this issue at some time in the future pending clarification by the court.

8. One comment suggested that FDA exempt manufacturers from the requirements set forth in this part if the new use that is the subject of the information being disseminated has been

accepted as standard medical practice (i.e., indications listed in the United States Pharmacopoeia Drug Information for the Health Care Professional (USP DI) or American Hospital Formulary Service, etc.).

FDA declines to create an exemption from the entire rule as suggested by the comment. Regardless of whether the unapproved use is listed in the USP DI or American Hospital Formulary Service, the statutory requirements in sections 551 through 557 of the act apply to a manufacturer who intends to disseminate information on the unapproved use for an approved product to health care practitioners, pharmacy benefit managers, health insurance issuers, group health plans, or Federal or State governmental agencies. Evidence that the unapproved use represents standard medical care may, however, enable the manufacturer to seek an exemption from the requirement to submit a supplemental application for the unapproved use if the manufacturer can demonstrate that it would be unethical to conduct the studies necessary for a supplemental application for the new use. A discussion of the ''unethical'' exemption appears later in section III of this document.

9. Some comments stated that the proposal properly reflects the intent of Congress and achieves the important goals of assuring the public health and encouraging the dissemination of information. Others argued that the proposal is contrary to congressional intent, paternalistic and cumbersome, and would restrict, rather than facilitate, access to information about new uses.

Although FDA drafted the proposed rule to reflect congressional intent, the agency has revised the rule in response to specific comments. These revisions are meant to ensure that the final rule more accurately reflects congressional intent.

B. Comments on Specific Provisions

1. Subpart A—General Information

a. Scope (§ 99.1). Proposed § 99.1 described the scope of part 99, explaining that the part applies to the dissemination of information on human drugs, including biologics, and devices where the information to be disseminated pertains to the safety, effectiveness, or benefit of a use that

is not included in the approved labeling for an approved drug or device or in the statement of intended use for a cleared device and the information is to be disseminated to a health care practitioner, pharmacy benefit manager, health insurance issuer, group health plan, or Federal or State Government agency.

10. Several comments urged FDA to add pharmacists to the list of recipients of information under this part.

Section 401 of FDAMA specifically lists who can receive the new use information under this provision and proposed § 99.1 tracked that statutory provision. Therefore, FDA declines to amend the regulation as requested. However, to the extent that pharmacists fall within the definitions of ''health care practitioner,'' ''pharmacy benefit manager,'' health insurance issuer,'' or ''group health plan'' (see § 99.3) they will be included as recipients of this information.

b. Definitions (§ 99.3). Proposed § 99.3 defined various terms, such as ''clinical investigation'' (proposed § 99.3(b)), ''health care practitioner'' (proposed § 99.3(d)), ''new use'' (proposed § 99.3(g)), ''scientific or medical journal'' (proposed § 99.3(i)), and supplemental application (proposed § 99.3(j)).

11. One comment urged FDA to include a definition for ''pharmacy benefit manager'' and to include pharmacists in that definition.

Although the statute defines the other recipients of information under this provision (i.e., health care practitioner, health insurance issuer, and group health plan), it does not define pharmacy benefit manager. FDA has revised the rule to define a ''pharmacy benefit manager'' (PBM) as ''a person or entity that has, as its principal focus, the implementation of one or more device and/or prescription drug benefit programs.'' PBM's, which generally include pharmacists, typically provide claims processing services for devices and/or prescription drugs; negotiate device and/or prescription drug prices; negotiate volume purchase agreements with medical device and/or pharmaceutical manufacturers, develop formularies, and institute formulary compliance programs

(e.g., mandatory generic substitution programs). The new definition is in § 99.3(h) and the agency has redesignated the remaining definitions accordingly.

12. Proposed § 99.3(b) defined a ''clinical investigation'' as an ''investigation in humans that is prospectively planned to test a specific clinical hypothesis.'' Several comments argued that FDA should delete the proposed definition of ''clinical investigation.'' They argued that restricting clinical investigations to those that are prospectively planned is not part of the statute, that it would preclude the use of retrospective studies, modeling studies, open label studies, metanalysis, reference articles, and consensus standards, which these comments assert may be useful, and that Congress never intended for the definition to be limited in this manner. One comment argued that the prospective planning criteria should not have to meet the criteria for investigational new drug applications (IND's).

FDA believes that many of these comments misconstrued what the agency meant by the phrase ''prospectively planned.'' FDA does not consider modeling studies, which are not actual studies, but rather extrapolations of information or data that are used to predict how a study might come out, to be clinical investigations. Moreover, FDA does not consider consensus standards and reference articles to contain adequate detail about ''clinical investigations'' as defined by this rule. However, it was the agency's intent that the definition could include historically controlled studies, retrospective analyses, open label studies, and metanalyses if they are testing a specific clinical hypothesis. To avoid any confusion, FDA is eliminating the phrase ''prospectively planned'' from the definition of ''clinical investigation.'' In the final rule, FDA has defined a clinical investigation to mean ''an investigation in humans that tests a specific clinical hypothesis.''

13. Several comments urged FDA to revise the definition of ''health care practitioner'' in § 99.3(d) to include pharmacists.

Section 556(1) of the act (21 U.S.C. 360aaa-5(1)) defines the term ''health care practitioner'' to mean a physician, or other individual who is a provider of health care, who is licensed under the law of a State to prescribe drugs or devices.'' FDA's proposed regulation tracked this statutory

definition. FDA declines to revise the definition. To the extent that pharmacists fall within this definition, they will be eligible to receive information disseminated under this part.

14. Proposed § 99.3(g) defined ''new use'' to mean a use that is not included in the approved labeling of an approved drug or device, or a use that is not included in the statement of intended use for a cleared device. The preamble to the proposed rule explained that a new use is one that would require approval or clearance of a supplemental application in order for it to be included in the product labeling.

The preamble to the proposed rule explained that ''new uses,'' include, but are not limited to: A completely different indication; modification of an existing indication to include a new dose, a new dosing schedule, a new route of administration, a different duration of usage, a new age group (e.g., unique safety or effectiveness in the elderly), another patient subgroup not explicitly identified in the current labeling, a different stage of the disease, a different intended outcome (e.g., long-term survival benefit, improved quality of life, disease amelioration), effectiveness for a sign or symptom of the disease not in the current labeling; and comparative claims to other agents for treatment of the same condition (see 63 FR 31143 at 31145).

A number of comments supported FDA's definition of new use. However, others disagreed with the specific examples set forth in the preamble as too broad. Most of the latter comments objected to the inclusion of patient subgroups and comparative claims for approved indications. They argued that their inclusion in the definition is inconsistent with the agency's prescription drug advertising regulations, which permit companies to promote patient subgroups and comparative claims if certain conditions are met. Several comments disagreed with the inclusion of a new age group—specifically children—in the definition of new use. One comment argued that children should not be considered a ''use,'' but a ''user.'' One comment stated that the definition should focus only on information that differs from the current labeling; it should not include information that is consistent with, but more detailed than what is described in the approved

labeling. Finally, one comment disagreed with the agency's characterization of a different intended outcome as an off-label use.

FDA agrees with the comments discussed previously, which note that FDA's prescription drug advertising regulations permit companies to make comparative claims about two approved uses, without getting the claims on the approved label if the companies have on file, substantial evidence or substantial clinical experience to support such claims. (See § 202.1(e) (21 CFR 202.1(e)).) FDA did not intend to change the provision found in its prescription drug advertising regulations. In addition, FDA agrees that as long as the comparison is between two approved claims, there technically is not a new ''use'' involved. Therefore, FDA is deleting comparative claims about approved uses from its interpretation of ''new use.'' Manufacturers who want to make such claims for a drug, must submit a labeling supplement or must meet the requirements set forth in FDA's drug advertising regulations. (See § 202.1(e).) Manufacturers who want to make such claims for a medical device must meet the requirements set forth in §§ 807.81(a)(3)(ii) or 814.39 (21 CFR 807.81(a)(3)(ii) or 814.39).

With respect to claims of efficacy in a new patient subgroup, including a new age group, claims that are more detailed than the approved labeling, and claims that relate to different intended outcomes (as well as with respect to some of the other types of new use claims listed in the preamble to the proposed rule), FDA's prescription drug advertising regulations may permit companies to make such claims about prescription drugs in certain circumstances, without submitting a supplement, provided they have on file the required evidence to support the claim. (See § 202.1(e).) However, FDA does consider such claims, including claims regarding children, to be new uses in some cases. In cases where such claims constitute new uses, manufacturers also can use the procedures set forth in this part to disseminate journal articles and reference publications about those claims. For medical devices, manufacturers can use the procedures set forth in this part to disseminate journal articles and reference publications about these types of

claims. Otherwise, they must comply with the requirements set forth in §§ 807.81(a)(3)(ii) or 814.39.

15. Proposed § 99.3(i) (now redesignated as § 99.3(j)) defined ''scientific or medical journal,'' in part, as a journal that is indexed in Index Medicus. It excluded scientific and medical publications that are in the form of special supplements that have been funded in whole or in part by one or more manufacturers. One comment agreed that special supplements are not appropriate for dissemination under this part. One comment, however, stated that the definition was too narrow by requiring that the publication be listed in Index Medicus and by excluding special supplements.

The definition in FDA's rule, which excludes journals not indexed in Index Medicus and scientific and medical publications that are in the form of special supplements that have been funded in whole or in part by one or more manufacturers, tracks the statutory definition. (See section 556(5) of the act.) Accordingly, no changes to the final rule have been made.

16. Proposed § 99.3(j) (now redesignated as § 99.3(k)) defined ''supplemental application'' as a supplement to support a new use to an approved new drug application (NDA) for human drugs or a supplement to an approved license application for biologics. Several comments argued that the definition of a supplemental application for a drug should be expanded to include the possibility that a ''new use'' could require a new NDA rather than just a supplemental NDA. One comment claimed that there are certain review divisions in the Center for Drug Evaluation and Research (CDER) that require NDA's for all new uses.

There may be times when a manufacturer would be required to submit an NDA rather than a supplemental NDA to support a new use. In these instances, the unapproved use would not be covered by this part. However, it would not be appropriate to exclude new uses from this part merely because a review division assigns a new NDA number to the supplement for administrative convenience. In the latter instance, the difference would be in name only. Therefore, although FDA is declining to revise the regulation as suggested by the comments, FDA will treat

applications that have been assigned a new NDA number for administrative convenience as a supplemental NDA for purposes of this part.

17. One comment recommended expanding the definition of supplemental application to cover OTC drugs that are subject to a monograph.

As set forth previously, OTC drugs that are subject to a monograph are not covered by this provision. Therefore, FDA declines to expand the definition as requested.

18. For devices, proposed § 99.3(j) (now redesignated as § 99.3(k)) defined ''supplemental application'' as a new 510(k) submission, if the device that is cleared for marketing is the subject of a 510(k) submission, or a supplement to an approved premarket approval application (PMA), if the device that is marketed is the subject of an approved PMA. One comment recommended expanding the definition of supplemental application for devices to include a 510(k) to a 510(k) exempt device.

FDA agrees that the statutory provision covers 510(k) exempt devices and so has amended the definition of supplemental application accordingly.

19. Several comments disagreed with FDA's definition of supplemental application for devices because it did not include a PMA for a new use for a device on the market under section 510(k) of the act (21 U.S.C. 360(k)).

Because there are no supplemental applications for 510(k) devices, FDA could have interpreted the statute to exclude all 510(k) devices from the scope of the rule. FDA drew a distinction between those that require a new 510(k) and those that require a PMA because the agency determined that this was similar to the distinction between a supplemental NDA and an NDA (i.e., a supplemental NDA and a 510(k) are filed on products about which the agency has some accumulated knowledge and experience such that it is not required to start its review from scratch; an NDA and a PMA are filed for products about which the agency has no such accumulated knowledge or experience upon which to base a decision).

FDA disagrees with the comment that an original PMA submission should be included in the definition of ''supplemental application'' for a device that entered the marketplace through the 510(k) process. The 510(k) process and the PMA process are designed to provide different ways to market regulated products, are supported by a different extent and kind of data, and are predicated on different concepts of how to assure consumer protection.

A product entering the market via the 510(k) process does so because the agency agrees with the sponsor that the new device is substantially equivalent to a device commercially distributed before May 28, 1976, or to a newer predicate device for the same intended use. For a 510(k) product, the consumer protection objective of the act is met in part by the accumulated experience with the predicate devices and the review and establishment of the device category in the appropriate class and a modicum of device specific information. Information on manufacturing and premarket assurance of conformance to good manufacturing practices (GMP's) are not addressed. The agency does not, in the case of a 510(k), make an individual product determination of safety or effectiveness.

The act requires a PMA for a device for which there is a new intended use with no predicate, or which raises new issues of safety and effectiveness. Evidence required under a PMA is substantial and the sponsor must show, through the use of well-controlled clinical trials or, at the discretion of the agency, other valid scientific evidence, that there is a reasonable assurance the product is safe and effective for its intended use. As part of its review of a PMA, FDA reviews and audits clinical trial information and the GMP's employed by the manufacturer.

Allowing an original PMA submission to be regarded in this context as a supplement for a device already marketed under a 510(k) would undermine the statutory and regulatory requirements established to ensure the safety and effectiveness of products subject to PMA's. It would be analogous to applying the dissemination provision to new devices that were never legally marketed. For a PMA product, a new intended use supplement is intended to provide the agency with additional data supporting a new use for an approved device. It relies, in large part, on

information previously reviewed regarding product materials, biocompatibility, design, performance, and basic safety data. For a 510(k) product, a PMA would not be providing additional information; it would be providing all of the information.

To illustrate, a product not currently marketed, but that was marketed as a general use tool without any known labeling or identified product specific intended use in the 1960's preamendment period may be re-introduced through a 510(k) for that same (implied) intended general tool use (e.g., it ablates or thermally destroys tissue). The product will be regarded as an unclassified preamendment product. If a manufacturer wished to market it for a specific intended purpose where that new purpose creates a new use with attendant questions of safety and effectiveness of the new use, it must do so through a PMA. In a recent instance, a company sought to market its unclassified preamendment product, an interuterine probe for a cryosurgery machine (using freezing to thermally destroy tissue), for ablation of the uterine endometrium with ultrasound control of the location and extent of tissue being frozen to control excessive menstrual bleeding. By moving to a tissue and anatomic specific intended use and indication, as well as by incorporation of a new (external) control procedure, the manufacturer has created a new intended use. The product's underlying safety and manufacture have never been evaluated. Even the presumption that ultrasound measurement of the extent of tissue being frozen accurately predicts the extent of tissue necrosis and allows proper positioning of the probe remains unevaluated. Nevertheless, the comments would argue that this product could be the subject of an article or text disseminated under section 401 of FDAMA.

In passing section 401 of FDAMA, Congress intended to provide health care practitioners important scientific information about unapproved uses of approved products. The risks to the public of disseminating information in a case such as that described previously are closer to the risks from instances where there has never been an approved product than those for a new use of a previously approved product. FDA believes that these risks are far greater than those authorized by section 401 of FDAMA.

2. Subpart B—Information To Be Disseminated

a. Information that may be disseminated (§ 99.101). Proposed § 99.101 discussed the types of information concerning the safety, effectiveness, or benefit of a new use that a manufacturer may disseminate. For example, the proposal required (among other things) that the written information to be disseminated concern a drug or device that has been approved, licensed, or cleared for marketing by FDA and be in the form of an unabridged reprint or copy of a peer-reviewed scientific or medical journal article or an unabridged reference publication that pertains to a clinical investigation involving the drug or device and that is considered scientifically sound by experts who are qualified to evaluate the product's safety or effectiveness. Proposed § 99.101 also described criteria for determining whether the information to be disseminated is false or misleading, whether a clinical investigation is ''scientifically sound,'' and whether a reprint or copy of an article or reference publication is ''unabridged.''

20. One comment urged FDA to include a 60-day window in advance of a drug's Prescription Drug User Fee Act date during which time a manufacturer could submit proposed material for review. In other words, the comment urged FDA to accept dissemination materials for review before a drug has been approved.

FDA declines to adopt this approach. The statute does not direct FDA to accept submissions on products that have not yet been approved or cleared. If FDA accepts submissions on products that have not yet been approved or cleared, it may be wasting resources reviewing submissions on products that never get approved or cleared.

21. One comment urged FDA to make clear that this part does not permit the verbal dissemination of unapproved use information. Another comment suggested that companies that disseminate information on a new use should be permitted to discuss the clinical investigation that is the subject of the disseminated materials with the recipient.

FDA agrees with the first comment that neither this part nor section 401 of FDAMA, would permit the verbal dissemination of information about unapproved uses. Section 551(a) of the act

and § 99.101 refer clearly and specifically to ''written'' information. Therefore, a manufacturer (or its representatives or agents) is not permitted to discuss with a recipient the clinical investigation that is the subject of the written materials disseminated under this part.

22. Several comments asked whether Internet or electronic dissemination would be permitted under this part.

Although, as set forth previously, FDA agrees that the provision was not meant to cover verbal dissemination, it could cover electronic dissemination. However, a manufacturer seeking to disseminate information electronically would have to ensure that all of the requirements under this part could be met for electronic dissemination. For example, the manufacturer would have to ensure that the recipients of the information are appropriately limited and that all of the required information and disclosures can be attached in accordance with this part. FDA may, in the future, issue guidance on this subject.

23. One comment noted the importance of requiring manufacturers to disseminate unabridged journal articles so that information from a clinical study is not pulled out of context or released without all relevant data.

FDA agrees with this comment. Both the statute and the regulation require that a journal article or reference publication disseminated under this part be unabridged.

24. Several comments objected to the requirement that a reprint or copy of an article be published prior to submission for FDA for review. These comments argued that manufacturers should be allowed to send FDA final manuscripts. Another comment opposed allowing submissions to include manuscripts or preprints of articles that have been accepted for publication. This comment stated that it could take months for these manuscripts to be published and that they might be submitted before the peer-review process is complete.

FDA understands manufacturers' desire to disseminate new use information as quickly as possible. However, section 552 of the act (21 U.S.C. 360aaa-1) requires that the peer-reviewed journal articles disseminated under this part be published. If FDA were to accept manuscripts before

publication, it could not be sure that what gets published, and then disseminated, is exactly what it was given to review. The agency might not even be sure that the peer-review process has been completed. FDA does not have the resources to verify this information or to conduct duplicative reviews. Therefore, FDA is not revising the rule to permit submission of unpublished manuscripts.

25. Several comments took issue with the statement in the proposal that information can be false or misleading if it includes only favorable publications. These comments argued that dissemination should not be prohibited if the only information that has been published is favorable and the research is scientifically rigorous. These comments noted that FDA should make clear that a single favorable publication can be disseminated if it is objective, balanced, and discusses appropriate safety information. One comment noted that a more appropriate manner in which to state the issue would be to cite the exclusion of an unfavorable publication as the example.

FDA agrees that new use information is not necessarily without balance or misleading just because there is no unfavorable information disseminated with it and FDA did not intend to suggest the contrary. FDA agrees that it would be inappropriate to find a favorable article misleading just because it is disseminated without an unfavorable publication when no unfavorable publication exists. What FDA will be looking for is whether the manufacturer has failed to include unfavorable information that exists and that is necessary to provide balance. FDA has revised the rule to clarify this point.

26. One comment said that proposed § 99.101(a)(4) was unclear on what ''other information concerning risks and adverse effects that are or may be associated with the new use'' a company would have to include to ensure that the disseminated information is not false or misleading.

The other information refers to the additional information that FDA can require under § 99.103(a)(4). FDA has revised the rule to clarify this point.

27. Proposed § 99.101(a)(5) required that the disseminated information not be derived from clinical research conducted by another manufacturer unless the manufacturer disseminating the information has the permission of such other manufacturer to make the dissemination.

One comment noted that the rule should clarify that contracts or agreements between sponsors may specify how the data are to be used by the sponsoring companies. In other words, cosponsoring companies should be responsible for maintaining their own agreements without FDA input. Several other comments opined that once a peer-reviewed article is published, it is in the public domain and a sponsor should be able to pursue use of the data published by the original sponsor (i.e., without first obtaining permission) as long as proper credit is given. One comment asked FDA to clarify the rule to show that research conducted by an independent academic or similar organization can be disseminated if the information meets the standards for dissemination and is legally available for such use.

Section 551(b)(3) of the act prohibits the dissemination of information derived from research conducted by another manufacturer without that other manufacturer's permission. The fact that an article has been published does not eliminate the need to get permission from the researching company. If it did, this requirement in the statute would be meaningless because all information disseminated under this part must be published. Therefore, FDA declines to revise the rule to permit the dissemination of all published articles reporting on research conducted by another manufacturer without that manufacturer's permission. However, FDA agrees that cosponsoring companies can make agreements without FDA's input and that research conducted by independent parties does not, by the terms of the statute, require that party's permission.

28. One comment noted that reference publications will include many unapproved use discussions that reflect research conducted by other manufacturers and that proposed § 99.101(a)(5) would appear to make the disseminating company get permission from every one of those manufacturers.

As set forth in the proposal, FDA expects that manufacturers that disseminate reference publications under this part will flag the section of the text that describes the clinical investigation of a specific unapproved use (otherwise, they would have to commit to study all of the unapproved uses discussed in the reference publication). Therefore, FDA would expect that a manufacturer

would be required only to seek the permission of another manufacturer if that other manufacturer conducted the study for that specific discussion of an unapproved use.

29. Proposed § 99.101(b)(1) provided that the determination of whether a clinical investigation is considered to be ''scientifically sound'' will rest on whether the design, conduct, data, and analysis of the investigation described or discussed in a reprint or copy of an article or in a reference publication reasonably support the conclusions reached by the authors. It further provided that a clinical investigation described or discussed in an article or reference publication must include a description of the study design and conduct, data presentation and analysis, summary of results, and conclusions pertaining to the new use. The proposal also stated that a clinical investigation presented in a format that does not represent a reasonably comprehensive presentation of the study design, conduct, data, analyses, and conclusions (e.g., letters to the editor, review abstracts, abstracts of a publication) would not qualify for dissemination under this provision.

The preamble to the proposal provided that in order to provide a basis for determining whether the conclusions are reasonably supported and the findings represent evidence of safety and effectiveness of the new use, the article or reference publication should provide, where applicable, evidence that the investigation: (1) Was prospectively planned; (2) enrolled an appropriately defined and diagnosed patient population for the specific clinical condition of interest; (3) accounted for all patients enrolled, including all patients who discontinued therapy prematurely; (4) utilized clinically meaningful endpoints or utilized surrogate endpoints that are reasonably likely to predict safety and effectiveness; (5) used a well described treatment regimen with a clear description of dose, schedule, duration, and route of administration; (6) used an appropriate control group or made reference to an appropriate historical control; (7) collected and reported adequate information on adverse experiences, and the need for dose reductions and treatment interruptions due to toxicity; and (8) was analyzed in a scientifically appropriate manner. (See 63 FR 31143 at 31146 and 31147.)

Some comments supported FDA's interpretation and applauded the agency's efforts to ensure that journal articles and reference publications are scientifically sound. These comments noted that FDA's interpretation reflected what is required by most peer-reviewed journals.

In contrast, a number of comments objected to FDA's approach. Some of these comments objected to FDA making any determination that an article or reference publication is scientifically sound. They stated that it was not Congress' intent to have FDA ''do its own peer review.'' Others criticized the criteria set forth in the proposed codified language and/or the eight criteria in the preamble to the proposal. They argued that FDA would be requiring more detail than is ever found in articles or reference publications and/or that FDA's standard is akin to that for a supplemental application. One comment said that FDA should require only enough detail to determine if the article or publication is scientifically sound. One comment urged FDA to adopt a broader definition of scientifically sound by removing the specific requirements, i.e., prospectively planned, and recognizing the value of scientifically sound studies as long as any limitations (e.g., epidemiological data) are fully disclosed. One comment said that FDA should require the journal article to include the ''typical level of detail'' and, if it does not, then the company should be able to attach it to the article. Several comments opposed the specific exclusion of abstracts. Finally, a number of comments specifically criticized the requirement that the clinical investigation be prospectively planned.

FDA has a role to play with respect to whether an article or reference publication is scientifically sound. The statute includes a requirement that the disseminated article or reference publication pertain to a clinical investigation that would be considered to be scientifically sound by experts qualified by scientific training or experience to evaluate the safety or effectiveness of the drug or device involved. FDA believes that this provision indicates that Congress meant for FDA to look at whether experts would find that the article or publication is about an investigation that experts would consider to be scientifically sound. However, FDA also believes that its role in determining whether an article or publication is scientifically sound is limited. This approach

is consistent with the proposed rule and FDA fully expected that most journal articles about a clinical investigation from reputable peer-reviewed journals would meet the definition of scientifically sound set forth in its proposal. Nevertheless, to ensure that the provision will be implemented consistent with congressional intent, FDA is revising § 99.101(b)(1) to provide that FDA will find that all journal articles and reference publications (as those terms are defined in § 99.3) are scientifically sound except: (1) Letters to the editor; (2) abstracts of a publication; (3) those regarding Phase 1 trials in healthy people; (4) flagged reference publications that contain little or no substantive discussion of the relevant clinical investigation; and (5) those regarding observations in four or fewer people that do not reflect any systematic attempt to collect data, unless the manufacturer demonstrates to FDA that such reports could help guide a physician in his/her medical practice.

Section 552(a)(2) of the act prohibits the dissemination of information that is false or misleading. That provision prohibits the dissemination of journal articles and reference publications that contain conclusions that are not supported by the study results. FDA has revised § 99.101(a)(4) accordingly.

30. One comment asked what FDA would do if an article discussed multiple unapproved uses, but the manufacturer wanted to focus on just one unapproved use.

FDA expects that there may be articles that discuss multiple unapproved uses and that such articles may be disseminated only if the requirements are met for each of those uses. There also may be instances when an article discusses multiple unapproved use(s), but there is one (or more) predominant unapproved use(s) discussed in the article. Under certain circumstances, it may make sense for the manufacturer to have to meet the requirements set forth in this part only for the predominant use(s). However, FDA will have to make this determination on a case-by-case basis.

31. One comment argued that dissemination of reference publications is not consistent with the purpose of section 401 of FDAMA because, by their very nature, reference publications are considerably out of date at the time of their publication. The comment further opined that because

the authors do not report the methods used to assess the current scientific literature, reference publications should be considered the authors' opinion and thus, not scientifically sound.

FDA agrees that many reference publications may not be up to date. However, Congress did include reference publications within the scope of section 401 of FDAMA. There is no basis to presume that all reference publications are not scientifically sound.

32. Several comments opposed the requirement that disseminated information in the form of a reference publication ''pertain to a clinical investigation regarding the drug or device.'' Instead, they argued, the reference publication should ''include information about'' such a study. Some comments interpreted this to mean that the study should meet all of the criteria to establish scientific soundness, but the information about such a study should not be required. One comment said that the language means that the information needs to be based on a scientifically sound clinical investigation, it need not be about or describe such clinical investigation.

Both the act and this part provide that reference publications must ''include information about a clinical investigation.'' However, this does not mean that the information about that clinical investigation should be any less complete than the information included in a journal article. It means only that the text may have a lot of additional information that is not about the clinical investigation. The idea behind the dissemination provision is that physicians and other recipients be in a position to make treatment decisions based on published reports of clinical trials. If the information that is disseminated gives them little or no information about the actual trial, then it would be difficult to argue that they have a reasonable basis upon which to make such treatment decisions.

33. A number of comments argued that the proposal has written reference publications out of the statute by requiring the same level of detail as would appear in journal articles. One comment said that FDA should accept the dissemination of peer-reviewed reference publications. Some comments argued that the proposal would make text book dissemination more difficult than it was prior to passage of FDAMA and that FDA should adopt a final rule that is consistent with

its existing reference text guidance or it should leave that guidance in place. One comment argued that the statute makes it clear that FDA must allow the dissemination of reference publications that meet the requirements of the statute and that the agency's decision to issue a guidance document on this issue is not an option.

As set forth previously, FDA does not believe that Congress meant that reference publications disseminated under this part could have less detail about clinical investigations than journal articles. In addition, reference publications are not subject to classic peer-review. Therefore, FDA rejects the comment that FDA accept all peer-reviewed reference publications. As discussed in the preamble to the proposal, however, FDA recognizes that it will be difficult for many reference publications to meet the statutory criteria. Moreover, as set forth in many of the comments, the new statutory scheme in most respects makes it more difficult to disseminate reference publications than was possible before FDAMA. Thus, FDA plans to permit companies to distribute unabridged reference publications (as defined in the statute and § 99.3(i)) without meeting all of the requirements set forth in this part if the company does not focus on or point to a specific unapproved use in the publication and it includes a disclaimer that the publication includes information about unapproved uses. (Cf. Guidance for Industry Funded Dissemination of Reference Texts (61 FR 52900, October 8, 1996). The agency was enjoined from applying this guidance document in *WLF* v. *Friedman*. FDA sought clarification on the scope of the order in that case through a motion to amend the judgment.) FDA plans to issue guidance on this issue at some time in the future following clarification by the court. Of course, manufacturers that want to focus or point to a specific unapproved use will have the option of doing so by meeting the requirements set forth in this part.

34. One comment argued that Congress intended for manufacturers to be able to disseminate reference publication chapters.

Section 552(a)(1) of the act clearly requires that the reference publication be unabridged. A chapter from a textbook does not meet this requirement.

35. Proposed § 99.101(b)(2) provided that journal articles and reference publications disseminated under part 99 cannot be disseminated with any information that is promotional in nature. One comment strongly agreed with the concept of prohibiting promotional material to be distributed with scientific information on a new use. One comment opposed the concept, stating that there is no policy or legal rationale for prohibiting companies from distributing information on approved uses with these reprints. A number of comments requested clarification of this statement. These comments were concerned that it could preclude a sponsor from delivering a promotional piece on a labeled use during the same office visit or detail. These comments suggested that FDA clarify that so long as the promotional material concerns an approved use and is kept physically distinct from the unapproved use information, FDA would not consider the two to be distributed together.

FDA did not intend to prohibit a sponsor from delivering promotional pieces on an approved or cleared use during an office visit or detail in which it has delivered information on an unapproved use. Any unapproved use information, however, must be kept physically distinct from the promotional materials, and the sponsor may not verbally promote the unapproved use or include materials about the unapproved use, beyond those permitted or required under this part.

b. Mandatory statements and information (§ 99.103). Proposed § 99.103 described the information that must accompany the journal article or reference publication. For example, it required a prominently displayed statement disclosing (among other things) that the information being disseminated is about a use that has not been approved or cleared by FDA and is being disseminated under section 551 *et seq.* of the act and, if applicable, a statement that there are products or treatments that have been approved or cleared for the use that is the subject of the dissemination. It also required the official labeling and a bibliography of other articles to accompany the disseminated information. In addition, the proposal described what is meant by a ''prominently displayed'' statement by setting forth criteria that are consistent with the agency's regulations on prescription drug advertising (§ 202.1(e)(7)(viii)) and labeling (21 CFR

201.10(g)(2)). Proposed § 99.103 required the statement that the use has not been approved and the additional information required by FDA to be attached to the front of the disseminated materials and that all other mandatory information be attached to the disseminated information.

36. Although some comments supported FDA's position on mandatory statements, there were others that thought the proposal was unduly restrictive. For example, although some comments supported the requirement for a uniform statement disclosing that the new use has not been approved by FDA, there were a number of comments that thought manufacturers should be allowed to use alternative language to convey this message. One comment specifically objected to the phrase ''and is being disseminated under section 551 of the Federal Food, Drug, and Cosmetic Act.'' This comment said that the phrase was unnecessary and could be confusing.

FDA continues to believe that it is important to have a uniform disclosure stating that the new use has not been approved by FDA. Different statements can be confusing and recipients of the information may believe that they have different meanings. FDA agrees, however, that the phrase: ''and is being disseminated under section 551 *et seq.* of the Federal Food, Drug, and Cosmetic Act'' is unnecessary and has therefore dropped it from the final rule.

37. One comment stated that clarification is needed regarding articles that discuss more than one use because, as written, § 99.103(a)(1)(i) uses singular and plural forms in a way that is confusing.

FDA agrees that clarification was needed and has revised the final rule accordingly.

38. Proposed § 99.103(a)(1)(iii) required a statement disclosing any authors who have a significant financial interest in the manufacturer. One comment noted that, although the disclosure is appropriate, the final rule should make clear that such disclosure be in line with the level required by the rule on financial disclosure and should apply only to the financial interests at the time the study was conducted and not the author's current interest.

In the preamble to the proposed rule, FDA stated that an author would have a significant financial interest in a manufacturer when there is a relationship that may give rise to actual or

perceived conflicts of interest and that when there is a question as to whether a relationship is significant, it should be disclosed (see 63 FR 31143 at 31147). Manufacturers may consult the final rule on financial disclosure by clinical investigators (codified at 21 CFR part 54) to learn the types of financial interests of greatest concern to the agency. However, because the purposes and terminology of this final rule and the final rule on financial disclosure by clinical investigators are different, manufacturers should consult the provisions of this final rule for the requirements that apply to disclosures regarding authors. FDA agrees that the financial disclosure should not necessarily apply to the author's current financial interest. FDA believes, however, that it should apply to the author's financial interests during the time the study was conducted up through 1 year after the time the journal article or reference publication was written and published. FDA has revised the final rule to reflect this time limitation. FDA's revision is consistent with part 54.

39. One comment urged FDA to require that the statement that there are products or treatments that have been approved or cleared for the use that is the subject of the dissemination list the names of other drugs that have been approved by FDA. Another comment asked whether such statement should address adjuvant or supporting therapies.

FDA's regulation tracks the statute, which does not require a manufacturer to identify the specific products that have been approved or cleared for the new use or the adjuvant or supporting therapy for the new use. (See section 551(b)(6)(A)(v) of the act.) Although FDA can see the benefit of having those specific product names listed, it would be difficult to develop a complete and accurate list. Moreover, the information could be misleading if the manufacturer merely provided a list of names. FDA also does not believe that the statement should address adjuvant or supporting therapies. The idea behind the disclosure is to let health care practitioners and other recipients know that approved/cleared alternatives exist. Therefore, FDA is retaining the requirement that the manufacturer only disclose that such approved/cleared products exist.

40. Proposed § 99.103(a)(2) provided that the manufacturer must attach the official labeling of the product to the unapproved use information. In the preamble to the proposed rule (63 FR 31143 at 31147), FDA noted that devices, unlike drugs, do not always include a package insert in the same form and manner as drugs. Therefore, the agency would expect device manufacturers to provide the same information that is generally found in package inserts, namely: (1) The name of the device, including its trade or proprietary name; (2) the manufacturer's name, address, and telephone number; (3) a statement of intended use, including a general description of the diseases or conditions that the device is intended to diagnose, treat, cure, or mitigate; (4) a description of the patient population for which the device is intended; (5) a description of indications that have been approved or cleared by FDA; (6) a description of any limitations or conditions that have been placed on the sale, distribution, or use of the device; and (7) all warnings, contraindications, side effects, and precautions associated with the use of the device.

One comment suggested that a device's official labeling be interpreted as: (1) The package insert for the device; (2) the accompanying documents that a manufacturer distributes with its legally marketed device to comply with the requirements of 21 CFR 801 or 809.10 for in vitro diagnostic products; or (3) the new labeling vehicle created by a manufacturer that contains the listed items from the preamble.

FDA agrees that this interpretation of official labeling for devices is appropriate provided the third option is used only when the first two options are not available or not feasible and provided the third option includes only the information listed in the preamble (i.e., no promotional statements or representations are included).

41. Proposed § 99.103(a)(3) required the manufacturer to attach a bibliography of other articles (that concern reports of clinical investigations both supporting and not supporting the new use). One comment noted that a bibliography is not required every time—only when one is not present in the disseminated information. Another comment stated that the bibliography requirement is vague

regarding what needs to be included and under what circumstances a bibliography included in the publication is sufficient.

FDA's proposal provided that the manufacturer need not include a separate bibliography if the disseminated information already includes a bibliography that meets the requirements set forth in § 99.103(a)(3). The bibliography requirement would be met by a list of all other published articles from scientific reference publications or scientific or medical journals that discuss clinical investigations and are specific to the new use discussed in the disseminated information. The bibliography must include articles about clinical investigations that both support and do not support the new use and it must identify which articles relate to the new use. A bibliography already included with the disseminated information would meet this requirement only if it includes all other such published articles. The manufacturer would still have to include its search strategy to show that it took reasonable steps to ensure that the bibliography includes all relevant published articles as described in § 99.103(a)(3).

42. Proposed § 99.103(a)(4) required a manufacturer to include any additional information required by FDA, including objective and scientifically sound information pertaining to the safety or effectiveness of the new use that FDA determines is necessary to provide objectivity and balance, including information that the manufacturer has submitted to FDA or, where appropriate, a summary of such information, and any other information that can be made publicly available; and an objective statement prepared by FDA, based on data or other scientifically sound information, bearing on the safety or effectiveness of the new use of the product.

Several comments noted that this provision should specify that FDA must provide the manufacturer notice and an opportunity to meet before requiring such information.

FDA agrees that a manufacturer must be provided notice and an opportunity to meet before being required to include this additional information. Redesignated § 99.301(a)(2) provides this opportunity and FDA has revised the final rule at § 99.103(a)(4) to include a reference to § 99.301(a)(2).

43. Several comments opposed the requirement that the statement that the use has not been approved and the additional information required by FDA be attached to the front of the disseminated materials and that all other mandatory information be attached to the disseminated information. One comment suggested that the FDA-required information be attached to the back, and that FDA permit the use of a sticker on the front of the disseminated material stating that the FDA-required information is attached to the back.

FDA believes that it is important to permanently affix the statement indicating that the disseminated information is about an unapproved use to the front of the materials. The recipients of such materials should know, in advance, that they are reading information about an unapproved use. However, FDA agrees that it could be appropriate to attach the additional information required by FDA to the back of the materials, provided there is a sticker or notation on the front referring the recipient to that information. The agency has amended § 99.103(a)(4) accordingly.

FDA also believes it is important to attach the remaining information to the disseminated materials. Congress included this mandatory information because it determined that it was important for the recipient to receive it. If such information is not attached, it can easily be separated from the disseminated material and never seen by the recipient. This is the information that helps to ensure that the disseminated materials are objective, balanced, and not misleading.

44. Although some comments stated that the criteria in proposed § 99.103(c) for determining whether the mandatory information is prominently displayed are appropriate, others opposed the factors that FDA will consider in determining whether the mandatory information is prominently displayed. The latter comments argued that manufacturers should retain some flexibility and discretion in this area.

FDA's approach is flexible. Section 99.103(c) sets forth the factors that FDA will consider and provides that the required statements shall be outlined, boxed, highlighted, *or otherwise graphically designed and presented in a matter that achieves emphasis or notice and is distinct*

from the other information being disseminated (emphasis added). Such an approach is not as proscriptive as the comments imply. FDA has retained this approach in the final rule.

45. One comment suggested that FDA permit manufacturers to post information, such as balancing articles required by FDA, on the Internet so long as the Internet address is prominently displayed on the information that was disseminated. The comment said that this would reduce paperwork burdens and provide a continuous source of current information.

FDA does not think that it would be appropriate for manufacturers to use the Internet to balance a published reprint disseminated in hard copy format or to provide recipients of unapproved use information with only part of the information required by the statute and regulations. The idea behind the provision was that physicians would receive, at one time, a balanced package. Such balance would not be achieved if a manufacturer could hand a physician an article and then advise the physician that he/she has to take steps on his/her own to retrieve the balancing information.

46. Several comments urged FDA to require manufacturers to provide patient labeling for drugs that are the subject of the disseminated information. The comments noted that such labeling should identify the drug by name, notify consumers that the drug has been promoted for an unapproved use, and indicate FDA-approved uses for the drug. They further argued that the patient labeling must include information about the potential risks of the drug and meet the quality and content standards of FDA's 1995 proposed Medication Guide rule. This comment said that FDA-approved patient labeling must be in commercial distribution at the level of the pharmacy before dissemination under this part can begin. One comment stated that the labeling should state that these products are not tested in certain populations and should say ''use at your own risk.''

FDA recognizes the importance of providing consumers access to information about the products they use. Since 1968, FDA has occasionally required and often encouraged manufacturers to produce patient labeling for certain prescription drugs. However, the comments' request for

additional patient labeling on drugs that are the subject of information disseminated under part 99 is outside the scope of section 401 of FDAMA.

47. Several comments argued that the lack of availability of pediatric studies on a particular use should be clearly and prominently stated in the information being disseminated to health professionals. These comments also urged FDA to require an additional statement for drugs that have not undergone pediatric testing: ''Safety and effectiveness in pediatric populations have not been established for this product for the use that has been approved by FDA or for the use suggested by this information.''

The suggestion that for drugs and devices that have not undergone pediatric testing, the disseminated information should include a statement to that effect is beyond the scope of this rule. However, for unapproved pediatric uses that are the subject of the information being disseminated, there will be a statement that the use has not been approved or cleared by FDA.

c. Recipients of information (§ 99.105). Proposed § 99.105 identified who may receive information disseminated under this part. Specifically, a health care practitioner, pharmacy benefit manager, health insurance issuer, group health plan, or Federal or State Government agency could receive information disseminated under part 99.

48. Several comments urged FDA to add pharmacists to the list of recipients of information under this part.

As previously discussed, section 401 of FDAMA specifically lists who can receive the unapproved use information under this provision. To the extent that pharmacists are included in the definitions of ''health care practitioner,'' ''pharmacy benefit manager,'' ''health insurance issuer,'' or ''group health plan'' (see § 99.3), they will be included as recipients of this information.

3. Subpart C—Manufacturer's Submissions, Requests, and Applications

a. Manufacturer's submission to the agency (§ 99.201). Proposed § 99.201 described the contents of a manufacturer's submission to FDA. This submission would be made 60 days before disseminating information on an unapproved or new use and would include items such as a copy

of all of the information to be disseminated, all other clinical trial information that the manufacturer has relating to the safety or effectiveness of the new use, any reports of clinical experience pertinent to the safety of the new use, and, if a supplement for the new use has not been submitted, a certification that the manufacturer will submit a supplement or an application for an exemption from the requirement to submit a supplement. The proposal also discussed what types of information must be submitted when the certification provides that the studies have been completed or that studies will be conducted as well as the contents of the certification. Proposed § 99.201 also provided that the 60-day period begins to run when FDA receives a complete submission.

49. One comment agreed that manufacturers should have to submit any clinical trial information that they have relating to the safety and effectiveness of the new use. However, another comment argued that the requirement for any clinical trial information is far more exhaustive than that required by the statute.

Section 551(b)(4)(B) of the act requires manufacturers to submit ''any clinical trial information the manufacturer has relating to the safety or effectiveness of the new use, any reports of clinical experience pertinent to the safety of the new use, and a summary of such information.'' Proposed § 99.201(a)(2) tracked this requirement and described what it included. In the final rule, FDA is making clear that, for effectiveness information, the requirements are limited to information on clinical investigations of the new use; safety information is broader and must include all relevant new data from human experience.

50. One comment urged FDA to require manufacturers to report only those adverse experiences that they have received directly because companies do not have access to the details of cases submitted to other manufacturers and thus, are unable to evaluate the reports. That same comment stated that FDA should permit adverse experience reports to be submitted in summary or tabular form rather than as individual case reports. Several other comments requested the ability to reference files that FDA already has about adverse experiences. Finally, one comment noted that the search requirements for adverse reports should be more clearly delineated.

Under the statute and these regulations, manufacturers would have to submit only those adverse experience reports that they have. This would include reports originally made to other manufacturers. If the reports were originally submitted to other manufacturers and the disseminating manufacturer does not know whether to attribute the adverse experience to the new use, it should submit the information to FDA. Manufacturers can submit adverse experience reports in summary or tabular form if FDA already has the individual case reports. With respect to search requirements for postmarket adverse event reports, FDA does not think that it is necessary to be any more specific. Manufacturers gather this information on a regular basis.

51. One comment said that the literature search requirements in § 99.201(a)(3) should be more clearly delineated. Several comments stated that the requirement for the submission of a search strategy is not required by statute and should be eliminated because it is unnecessary and burdensome and could delay the process.

FDA believes that it is necessary to include the search strategy. This is how FDA will be able to determine whether the bibliography meets the statutory criteria. FDA has revised § 99.201(a)(3), however, to clarify the bibliography search strategy requirements.

52. FDA, on its own initiative, revised § 99.201(a)(4)(i)(B) and (a)(4)(ii)(B) to clarify that, for purposes of computing time periods that begin on the date of initial dissemination, FDA will look to the date on which dissemination can begin. This clarification was necessary because FDA will not know when a manufacturer actually begins to disseminate materials. The same revision was made to §§ 99.203(b) and 99.401(b).

53. Proposed § 99.201(a)(4)(ii) required a manufacturer that has planned studies that will be needed for a supplement to submit the proposed protocols and schedule for conducting such studies. The protocols must comply with FDA's IND or investigational device exemption (IDE) regulations. One comment asked FDA to clarify whether a manufacturer who has planned studies and wishes to disseminate information must submit a complete IND or IDE in addition to the information required in a submission under this rule. One comment stated that if the protocols are to be treated

as IND's, IDE's, or amendments thereto, the manufacturer should be able to commence the studies within 30 days unless the agency places the study on clinical hold. The same comment said that if the agency does not place a clinical hold on the protocol within 30 days, the agency should not be able to determine that the protocols are inadequate on day 60 and if the protocol is put on clinical hold within 30 days, it should not be dispositive of the decision. The comment further stated that if the agency decides that the protocols are adequate, it should be bound by this decision and the final rule should reflect this. Finally, several comments urged FDA to permit manufacturers to cross reference IND's and IDE's rather than resubmitting such information.

FDA intends that the protocols for planned studies under this provision be submitted in compliance with the IND or IDE regulations. However, a manufacturer will not be required to submit these materials twice. If a protocol has already been submitted to an IND or IDE, the IND or IDE can be cross referenced in the dissemination submission.

Moreover, FDA does not intend to change, in any way, the IND or IDE regulations, including the timeframes. If an IND or IDE is submitted and a clinical hold is not issued within 30 days, the manufacturer can commence the study or studies. However, the fact that FDA does not issue a clinical hold within 30 days, does not prevent FDA from determining, within 60 days, that a protocol is inadequate. FDA can issue a clinical hold at any time after the 30-day period if the requirements for issuing a clinical hold are met. If the protocol is put on clinical hold within 30 days, it may not be dispositive of the issue because the sponsor may remedy the reason for the clinical hold within the 60-day period. However, if the reason for issuing the clinical hold is not resolved, it will be dispositive of the issue. Finally, FDA is declining to revise the rule to provide that if the agency finds that the protocols are adequate, it will be bound by this decision. FDAMA addressed the issue of agreements regarding the parameters of the design and size of clinical trials. (See, e.g., section 505(b)(4)(C) or section 520(g)(7)(A) through (g)(7)(C) of the act (21 U.S.C. 360j(g)(7)(A) through (g)(7)(C)).) FDA will abide by these statutory directives.

54. Proposed § 99.201 (a)(4)(ii) required a manufacturer that has planned studies that will be needed for the submission of a supplemental application for the new use to certify that it will exercise due diligence to complete such studies and submit a supplement within 36 months of dissemination. FDA has revised this section to reflect the possibility that FDA may determine, before the certification is submitted, that the studies needed to submit a supplemental application cannot be completed and submitted within 36 months. This change is further reflected in $99.203.

55. One comment requested that the 36-month timeframe for submitting a supplement not override the time limits created under separate regulatory or statutory authority. This comment was concerned that if FDA finalizes its proposed 1997 regulation on pediatric research and it includes compliance dates for completing the pediatric studies that are less than 36 months, the 36-month period in this part not override that shorter timeframe.

As FDA has stated elsewhere in this document, nothing in this regulation is meant to change or supersede other regulatory requirements.

56. One comment asked FDA to clarify the submission requirements and FDA action requirements with respect to nonsignificant risk devices.

Protocols submitted for studies for devices considered to be nonsignificant will be reviewed by FDA only to ensure that the protocol for the study is consistent with the new use information to be disseminated. Manufacturers must present the protocol for the nonsignificant risk device study to an institutional review board (IRB) for approval before starting the study. (See 21 CFR 812.1 (b)(l).) However, all reporting requirements under this part will apply to nonsignificant risk device studies.

57. One comment requested that the agency provide the sponsor an opportunity to meet with FDA promptly to review what changes can be made to the protocol to ensure that it meets requisite standards.

Sections 505(b)(4)(B) and 520(g)(7)(A) and (g)(7)(C) of the act provide sponsors with an opportunity to meet regarding their proposed protocols. Therefore, no changes to this rule are necessary,

58. One comment recommended that all statements submitted under this part be certified by an officer from the manufacturer's executive committee. Another comment recommended that the language in the certification should include "to the best of my knowledge" to reduce the risk that a certifying official could be penalized for an inadvertent mistake not within his/her knowledge.

The final rule requires that the manufacturer's attorney, agent, or other authorized official sign the submission. Although an officer from the manufacturer's executive committee may be an authorized official, FDA does not think it is necessary for the submission to be signed by such an officer. FDA also does not agree that it would be appropriate to include the words ''to the best of my knowledge" in the certification. The attorney, agent, or other authorized official who signs the submission and certification on behalf of the manufacturer, and ultimately the manufacturer itself, is responsible for what is submitted to the agency under this part.

59. Proposed § 99.201(c) described the component in each FDA center that will receive a submission under this part. Several comments noted that it would be appropriate for the review divisions in the centers to also receive copies of the information submitted under this part.

In the final rule, FDA is retaining the requirement that the submissions go to a single office within each center. Those offices will forward the information to the appropriate review divisions within the agency. The regulation need not spell out all of FDA's internal procedures for processing these submissions.

60. One comment stated that FDA needs to clarify the required physical organization of the documents submitted under this part.

FDA does not think it is appropriate to include that kind of detail in this regulation. Nevertheless, FDA expects that materials in a submission will be organized and labeled in

accordance with the submission requirements described in this part. If FDA subsequently determines that manufacturers need more guidance in this area, it will issue a guidance document.

61. A number of comments objected to proposed § 99.201(d), which provided that the 60-day (post submission) period shall begin to run when FDA receives a complete submission and that a submission shall be considered complete if FDA determines that it is sufficiently complete to permit a substantive review. These comments argued that FDA would use this provision to extend the 60-day time period. The concern was that FDA would, on day 59, advise a manufacturer that their submission was not complete and therefore the 60-day time period had not begun. The comments said that Congress meant for FDA to give a final answer within the 60-day time period.

As further described below, FDA is committing to give manufacturers a final decision within 60 days. FDA has revised § 99.201(d) to provide that the 60-day period shall begin when FDA receives a manufacturer's submission, including, where applicable, a certification statement or an application for an exemption.

62. A number of comments were made regarding the appropriateness of public disclosure of information submitted under this part. Some comments argued that both the fact of the submission and all information in the submission is confidential and should not be released. Other comments argued that all of the previous information should be public because the public, including the patient community, wants to be involved and has a right to know about a submission, the data in such submission, FDA action on the submission, what studies are being conducted, and the status of those studies. Several comments argued that upon receiving a submission, FDA should publish in the **Federal Register**, the citation for the article and the bibliography, and solicit additional published information that might be appropriate for dissemination. One comment argued that the public should have an opportunity to comment prior to FDA's granting approval for dissemination of information and that FDA should hold an advisory committee meeting and let the public participate in its decision on whether an exemption from the requirement to submit a supplement should be granted.

FDA declines to amend the rule to require a notice and comment process before permitting dissemination to proceed or before granting an exemption. However, the Freedom of Information Act (FOIA) and FDA's regulations will dictate what information submitted under this provision can be disclosed. Because the agency was required to issue this regulation within such a short period of time, it has been unable to fully examine all issues of disclosability. However, the agency will continue to examine these issues separately.

b. Request to extend the time for completing planned studies (§ 99.203). Section 554(c)(3) of the act (21 U.S.C. 360aaa-3) describes two types of extensions of time regarding planned studies. Section 554(c)(3)(A) of the act provides that the 36 month period for completing planned studies and submitting a supplemental application may be extended by the Secretary of Health and Human Services (the Secretary) if the Secretary determines that the studies needed to submit such application cannot be completed and submitted within 36 months. This type of extension would be granted before such studies are begun. Section 554(c)(3)(B) of the act provides that the period for completing planned studies and submitting a supplemental application may be extended by the Secretary if the manufacturer submits a written request for the extension and the Secretary determines that the manufacturer has acted with due diligence to conduct the studies in a timely manner. The latter extension cannot exceed 24 months. Proposed § 99.203 set forth the procedures that a manufacturer must follow to request an extension of time for submitting a supplemental application and the content of a request for an extension. The provision covered only the extension in section 554(c)(3)(B) of the act.

63. The comments to this provision indicated that there was some confusion regarding the two different statutory procedures. Several comments asked FDA to more clearly set out the two procedures contemplated by the statute.

Although the statute specifically refers to a manufacturer request in connection only with the procedure described in section 554(c)(3)(B) of the act and FDA agrees that the agency can, under section 554(c)(3)(A), on its own initiative determine before the studies have begun that more than

36 months is needed, FDA believes that manufacturers will come to FDA and ask FDA to make a determination under section 554(c)(3)(A) of the act. Therefore, FDA has revised § 99.203 to establish procedures for the two different types of extensions. The first extension, set forth in § 99.203(a), relates to a request for an extension by the manufacturer at or before the time it submits its dissemination package to FDA because the 36-month period is not enough time to complete a study or studies of the new use and submit a supplemental application. Revised § 99.203(b) sets forth the procedures that a manufacturer must follow to request an extension of time for submitting a supplemental application after a study has begun and the content of a request for an extension.

c. Application for exemption from the requirement to file a supplemental application (§ 99.205). Proposed § 99.205 set forth what a manufacturer must submit when seeking an exemption from the requirement to file a supplemental application for a new use for purposes of disseminating information on that new use. It required the manufacturer to include an explanation as to why an exemption is sought and to include materials demonstrating that it would be economically prohibitive or unethical to conduct the studies needed to submit a supplemental application for the new use.

64. A number of comments supported the standards that FDA proposed to determine whether it would be economically prohibitive or unethical to conduct the studies needed to submit a supplemental application. Some noted that FDA's standards are consistent with congressional intent that exemptions be limited in scope and infrequent or rare. One comment argued that pediatric exemptions should be extremely rare. One comment stated that exemptions should never be granted.

FDA agrees that Congress intended that exemptions from the requirement to file a supplemental application for a new use be granted in limited circumstances (see H. Conf. Rept. No. 399, 105th Cong., 1st sess. at 100 (1997); 143 Congressional Record S9,837 (daily ed. Sept. 24, 1997) (Statement of the Managers)). There is nothing in the statute or legislative history that gives FDA authority to apply a different standard in the case of pediatric exemptions. Moreover,

the act provides for exemptions, so FDA does not agree that such exemptions should never be granted. In light of the comments received to the standards set forth in its proposal (discussed in more detail below), FDA is adopting a different standard for the economically prohibitive exemption. Although, FDA is not changing the standard for the unethical exemption, it has, as discussed in the following paragraphs, clarified how it will apply that exemption.

Economically Prohibitive Exemption

Under proposed § 99.205(b)(1), a manufacturer seeking an exemption from the requirement to file a supplemental application on the basis that it would be economically prohibitive to conduct the needed studies would have to: (1) Explain why existing data, including data from the scientifically sound study described in the information to be disseminated, are not adequate to support approval of the new use; and (2) show, at a minimum, that the estimated cost of the necessary studies would exceed the estimated total revenue from the product minus the cost of goods sold and marketing and administrative expenses attributable to the product and that there are not less expensive ways to obtain the needed information.

Proposed § 99.205(b)(1) set forth the type of evidence that the manufacturer would have to include to meet the requirements for an economically prohibitive exemption. These included:

(1) A description of the current and projected U.S. patient population for the product and an estimate of the current and projected economic benefit to the manufacturer from the use of the drug or device in this population. The estimate would assume that the total potential market for the drug or device is equal to the prevalence of all of the diseases or conditions that the drug or device will be used to treat and involve the following considerations: (a) The estimated market share for the drug or device during any exclusive market period, a summary of the exclusive market period for the product, and an explanation of the basis for the estimate; (b) a projection of and justification for the price at which the drug or device will be sold; and (c) comparisons with sales of similarly situated drugs or devices, where available.

(2) A description of the additional studies that the manufacturer believes are necessary to support the submission of a supplemental application for the new use and an estimate of the projected costs for such studies; and

(3) An attestation by a responsible individual of the manufacturer verifying that the estimates included with the submission are accurate and were prepared in accordance with generally accepted accounting procedures. The data underlying and supporting the estimates shall be made available to FDA upon request.

65. As set forth previously, some of the comments agreed with FDA's construction of ''economically prohibitive'' These comments argued that such exemptions should be granted rarely and that the criteria for such an exemption should be rigorous. One comment argued that the cost for the studies should substantially exceed revenues to qualify for the exemption. Several comments opposed such an equation.

FDA agrees that exemptions should be granted only in limited circumstances. As set forth below, however, FDA was convinced by the comments that the standard set forth in its proposal was inappropriate and has revised the standard.

66. A number of comments objected to how the agency proposed to determine what is economically prohibitive. First, they objected to the agency's use of the term ''rare'' in describing when such exemptions would be granted. One comment opined that Congress meant for the exemption to arise in a ''fair number of circumstances.'' Second, they objected to the absence of the criteria listed in the statute and report language from the standard set forth in the codified regulation. Third, they claimed that the proposed rule's standard for determining what is economically prohibitive is too high.

One comment argued that the exemption should be granted if it does not make economic sense to pursue a supplement. Others argued that it should be based on the revenue from the new use, not all uses of the product. Some argued that the standard should be whether the cost of the studies would exceed the revenues from the new use; others argued that it should be whether

the cost of the studies exceeds the new use revenues that resulted from approval of the supplement (i.e., the increase in revenues from the new use that result from submission of the supplement). Several comments argued that FDA should automatically grant an exemption if the new use is for a rare disease or condition because for such use there is no reasonable expectation that the cost of developing and making available a drug for such disease will be recovered from sales in the United States of such drug. Several comments argued that the economically prohibitive exemption should automatically be granted if: (1) There is no market exclusivity for the product (from patent, orphan drug status, or Waxman-Hatch); or (2) the patient population likely to be served by the new indication will not exceed an established number (e.g., 1,000). One comment opined that interpreting ''prohibitive'' to mean anything other than the point at which an economically rational company will not pursue research ignores the needs of patients with rare disorders.

FDA agrees that Congress did not use the term ''rare'' in the legislative history. Nevertheless, Congress did state that exemptions to the requirement to submit a supplement would be appropriate only in ''limited circumstances,'' which in FDA's view implies fewer than in a ''fair number of circumstances.'' Moreover, Congress strongly emphasized the critical importance of getting information about new uses onto the label. Although FDA did not include the criteria listed in the statute and the legislative history in the standard for economically prohibitive, they were included as types of evidence that would be required to support the exemption.

FDA's proposed criterion did not focus solely on sales from the new use because the agency believed that there might be many circumstances where the cost of the study requirements would exceed the sales from just the new use. The agency explained that in some of these situations, even if it were not economically ''wise'' to conduct the studies, the cost would not rise to the level of being ''prohibitive.'' This view was judged consistent with the legislative history, which foresaw the granting of economic exemptions only in limited circumstances. The agency noted, however, that defining a practical ''economically prohibitive'' exemption was particularly

troublesome, because it would be so difficult for the agency to assess cost and income projections. In view of these difficulties, FDA acknowledged that it was not certain that the proposed approach was optimal and sought comment on other possible ways to define economically prohibitive.

Unfortunately, the agency has received widely conflicting public comment on this issue and remains uncertain about the elements of a standard that would be most appropriate and effective in achieving the statutory goals. An approach that would grant automatic exemptions if: (1) The new use were for a rare disease or condition; (2) there was no market exclusivity for the product (from patent, orphan drug status, or Waxman-Hatch); or (3) the patient population likely to be served by the new indication would not exceed an established number (e.g., 1,000) would be inappropriate. Neither the statute nor the legislative history provide for automatic exemptions in these circumstances. Rather, they direct FDA to take both market exclusivity and population size into account. The legislative history made clear that the size of the patient population would not necessarily justify an exemption. In fact, the legislative history stated that an exemption based on the size of the patient population was intended to be the exception rather than the rule in cases of populations suffering from orphan or rare diseases or conditions. The legislative history made clear that FDA should consider the importance of getting products for these diseases or conditions approved. It noted that for many years, Congress has sought to encourage research into orphan diseases and support the approval of innovative drugs for their treatment. Congress, therefore, has directed FDA to recognize the vital importance of encouraging applications for new products intended to treat rare diseases and to examine very carefully whether an exemption from filing a supplemental application might hinder such research (see H. Conf. Rept. No. 399, 105th Cong., 1st sess. at 100 (1997); H. Rept. No. 310, 105th Cong. 1st. sess. at 62 (1997)).

Because the agency remains uncertain about the elements of a standard that would be most appropriate and effective, FDA plans to continue its search for a policy that would satisfy the congressional expectation of approving exemptions in only limited circumstances, without foreclosing the dissemination of useful information by firms that could not otherwise conduct the

needed studies. In the meantime, FDA will implement the statute by basing its evaluation of each exemption on a case-by-case determination of whether the cost of the study for the new use reasonably exceeds the total expected revenue from the new use minus the cost of goods sold and marketing and administrative expenses attributable to the new use of the product. This standard may not always meet a strict profitability criterion because it considers all new use revenues, rather than just the new use revenues that would result from approval of the supplement. Nevertheless, it is consistent with most of the comments submitted by the affected industry on this issue, it is consistent with the statutory directive, and it attempts to strike a fair balance between assuring the widest possible information dissemination while granting economic exemptions only in ''limited circumstances.''

The final rule sets forth the statutory standard and the information that FDA would need to make this case-by-case determination. This will include information about: (1) The cost of the study for the new use; (2) the expected patient population for the new use; (3) the expected total revenue for the new use minus the cost of goods sold and marketing and administrative expenses attributable to the new use of the product; (4) the amount of exclusivity for the drug or new use; and (5) other information that the manufacturer believes demonstrates that conducting the studies on the new use would be economically prohibitive.

As this revised criterion may significantly expand the number of exemption applications beyond that anticipated by the Congress, the agency is determined to review its experience with these requests as they are submitted and, if necessary, to contract with outside economic experts to help develop an approach that most appropriate and effective and workable for the agency.

67. A number of comments objected to the requirement to submit detailed financial data. These comments argued that manufacturers should be not required to submit highly sensitive and proprietary information. Others felt that FDA is not qualified to review and evaluate this data.

Congress directed FDA to grant an economic exemption only upon making a determination that conducting the studies and submitting a supplement would be economically prohibitive. FDA

cannot make this determination without examining the relevant company data. Therefore, the final rule retains these requirements.

68. Several comments regarding FDA's approach to economic exemptions recommended that FDA require a manufacturer to submit a certified public accountant's (CPA's) opinion on the economic feasibility of filing a supplemental NDA. FDA could contest the claim by providing a CPA's statement to the contrary.

FDA declines to adopt this approach because it removes the agency from the statutorily-specified role of determining whether it would be economically prohibitive to conduct the studies.

69. One comment recommended that manufacturers be given the flexibility to present whatever information they determine is relevant to the ''economically prohibitive'' factor, that the manufacturer be able to use its own assumptions, and that each situation be evaluated on a case-by-case basis.

As set forth previously, FDA is adopting a case-by-case determination and has specified the information that is essential for this determination. Nevertheless, manufacturers are free to provide whatever additional information they think is relevant to the determination. This could include information that would explain why a study is so expensive to conduct. For example, one factor might be the difficulty of enrolling patients in a clinical investigation if the new use has become the standard of care.

70. Proposed § 99.205(b)(1)(ii)(A) stated that the estimated economic benefit for a drug or device shall assume that the total potential market is equal to the prevalence of the disease(s) or condition(s) that such product will be used to treat. Several comments argued that this assumption should be deleted because the potential market for the drug or device may be less than the prevalence of the disease in question if other therapies are likely to be used in some portion of the total patient population.

FDA agrees that this assumption should be deleted and has done so in the final rule.

71. One comment argued that the manufacturer should not be required to provide a ''justification'' of the price at which the drug will be sold. According to this manufacturer, only a projection is relevant.

FDA has to be able to determine whether the manufacturer's proposed price is reasonable. It may be that ''justification'' for the price is not appropriate. Therefore, in § 99.205(b)(ii)(C) of the final rule, FDA will seek an explanation of the price at which the drug or device will be sold.

72. One comment opined that permitting an exemption because of cost is an ethical decision because it is placing a monetary value on people's lives and safety.

FDA does not agree that an economically prohibitive exemption is placing a monetary value on people's lives and safety. The standard in FDA's regulation is intended to best effectuate the goals of the statute.

73. Proposed § 99.205(b)(1)(ii)(C) required a manufacturer to provide an attestation by a responsible individual of the manufacturer verifying that the estimates included with a submission are accurate and were prepared in accordance with generally accepted accounting procedures. In addition, the data underlying and supporting the estimates would have to be made available to FDA upon request. In the preamble to the proposed rule, FDA noted that it had considered requiring a report of an independent CPA with respect to the estimates and FDA solicited comment on whether such a report should be required in lieu of, or as an alternative to, the attestation that would be required by the proposal.

Some comments supported the submission of the CPA report discussed previously, others felt that such a report should not be required. Still other comments stated that the CPA report should be submitted in lieu of the underlying data or that the CPA should make the determination of economic feasibility instead of FDA.

As stated previously, FDA refuses to adopt a procedure by which it surrenders decision making to a CPA. However, FDA is not convinced that it is necessary to require a report of an independent

CPA with respect to the estimates. Under § 99.205(b)(1)(iii), therefore, FDA will accept either an attestation by a responsible individual of the manufacturer or by a CPA verifying that the estimates included with a submission are accurate and were prepared in accordance with generally accepted accounting procedures.

Unethical Exemption

Proposed § 99.205(b)(2) required a manufacturer seeking an exemption on the basis that it would be unethical to conduct the studies needed to submit a supplement, to: (1) Explain why existing data, including data from the scientifically sound study described in the information to be disseminated, are not adequate to support approval of the new use; and (2) show that, notwithstanding the insufficiency of existing data to support the submission of a supplemental application for the new use, the data are persuasive to the extent that withholding the drug or device in the course of conducting a controlled study would pose an unreasonable risk of harm to human subjects.

The proposed codified language provided that an unreasonable risk of harm would ordinarily arise only in situations in which the new use of the drug or device appears to affect mortality or irreversible morbidity. Evidence suggesting that the drug or device is the standard of care for the new use can add weight to an argument that conduct of a needed study or studies would be unethical.

To support its argument that the conduct of a needed study or studies would be unethical, the proposal provided that a manufacturer would need to address the possibility of conducting studies in different populations or of modified design (e.g., adding the new therapy to existing treatments or using an alternative dose if monotherapy studies could not be conducted).

The proposal further provided that in assessing the appropriateness of conducting studies to support the new use, the manufacturer may provide evidence that the new use represents standard medical treatment or therapy. Evidence that the new use represents standard medical therapy can be one element of an argument that studies cannot ethically be conducted, but the persuasiveness

of available data is equally important. Evidence that the new use represents standard medical therapy might be obtained from a number of different sources. The preamble to the proposal set forth the following possible considerations: (1) Whether the new use meets the requirements of section 1861(t)(2)(B) of the Social Security Act, which defines ''medically accepted indications'' with respect to the use of a drug; (2) Whether a medical specialty society that is represented in or recognized by the Council of Medical Specialty Societies (or is a subspecialty of such society) or is recognized by the American Osteopathic Association has found that the new use is consistent with sound medical practice; (3) Whether the new use is described in a recommendation or medical practice guideline of a Federal health agency, including the National Institutes of Health, the Agency for Health Care Policy and Research, and the Centers for Disease Control and Prevention of the Department of Health and Human Services; and (4) Whether the new use is described in a current compendia such as the United States Pharmacopoeia Drug Information for the Health Care Professional, the American Medical Association Drug Evaluations, or the American Hospital Formulary Service (see 63 FR 31143 at 31150).

74. A number of comments objected to FDA's proposed criteria for the unethical exemption—particularly the emphasis on the requirement that it ordinarily would arise only in situations in which the new use appears to affect mortality or irreversible morbidity. Some comments believed that the criteria set forth in the legislative history (that are discussed in the preamble) should be in the codified language. Finally, a number of comments argued that if the new use is the standard of medical care, FDA must automatically grant an exemption.

The act clearly does not require FDA to automatically grant an exemption if a new use is the standard of medical care. The act says that FDA must *consider (among other considerations that the Secretary finds appropriate*) whether the new use is the standard of medical care, and that is what FDA proposed to do. Moreover, an automatic exemption would not be reasonable from a scientific standpoint because there are many instances in which the results of a controlled

clinical trial have demonstrated that a drug or device is unsafe or ineffective for a new use for which it is considered to be the standard of care.

The standard set forth in § 99.205 is consistent with how FDA determines what studies are unethical in other contexts (i.e., when a manufacturer argues that it would be unethical to conduct a study). Moreover, the standard is consistent with the legislative history, which provides that such exemptions should be granted in limited circumstances. Therefore, FDA is retaining the proposed basic standard for the unethical exemption in the final rule (i.e., the data are persuasive to the extent that withholding the drug or device in the course of conducting a controlled study would pose an unreasonable risk of harm to human subjects). FDA continues to believe an effect on irreversible morbidity or mortality is what ordinarily would be required to show an unreasonable risk of harm. Nevertheless, there could be other circumstances in which the agency would find that it would be unethical to do the study, i.e., because there would be an unreasonable risk of harm even though the new use does not affect irreversible morbidity or mortality. In making a determination that it would be unethical to conduct a study, the agency must consider whether informed consent and proper IRB review would address the concerns raised by questions about whether it is appropriate to conduct a study.

FDA rejects the suggestion that the factors set forth in the legislative history that FDA may consider in deciding whether to grant an exemption be included as requirements in the codified language. FDA has included the statutory factors in the codified language. The legislative history provides that FDA may consider those factors among other factors, and thus, consideration of these factors is neither mandatory nor is it exclusive.

75. One comment argued that the standard needs to take into account the difficulty of enrolling patients in a study in which some subjects will receive a placebo when a patient can go to a doctor and receive a prescription for the drug. The comment further noted that physicians refuse to participate in placebo controlled studies of therapies they already believe to be effective.

FDA agrees that it can be difficult to enroll patients in placebo controlled trials and that this could be a relevant consideration. Moreover, not all controlled studies are placebo controlled. Companies may be able to conduct studies of a different design, depending on the situation. For example, a company may be able to compare the new use to another therapy that is known to work or may be able to rely on historical controls. In some cases, the new use could be added to existing therapy and compared with placebo added to existing therapy. If these alternate study designs mean that the study or studies will take longer, FDA can consider whether to extend the time to conduct the studies and submit a supplemental application.

76. One comment suggested that FDA should grant an exemption if the new use is listed in the USP DI or Hospital Formulary. Another comment suggested that an unethical exemption should be granted if the unapproved use: (1) Is accepted in a monograph of the USP; (2) is approved by another ''first world'' country; or (3) is approved by a state FDA. Finally, one comment suggested that FDA should automatically grant an unethical exemption if the new use: (1) Represents the standard of care, as represented by inclusion in specified compendia or practice guidelines, or (2) involves a combination of products or more than one sponsor and should grant other exemptions on a case-by-case basis.

FDA does not agree that any of these individual factors is enough to show that studying a new use would be unethical. Moreover, there is nothing in the statute or legislative history to suggest that any of the single factors should be sufficient to meet the unethical exemption. FDA will, however, consider these factors in making its determination of when it would be unethical to conduct a study.

77. One comment noted that, although it supported the list of sources to be used to provide evidence that a new use represents standard medical therapy, after 1998, the American Medical Association's (AMA's) Drug Evaluation and the USP DI may no longer be available.

If the AMA's Drug Evaluation and/or the USP DI become unavailable, FDA will stop using them as evidence that a new use is the standard of care.

78. One comment noted that there are diverse opinions in the medical community about what standard of care means. Another noted that ''consistent with sound medical practice'' is not the same as ''standard of care'' and that an unapproved treatment may be considered to be sound medical practice but should still be studied. Several comments noted that FDA should take care in how it interprets ''standard medical treatment or therapy.'' These comments noted that manufacturers should not be allowed to take advantage of a situation of their own creation. In other words, standard medical treatment should not be interpreted as meaning treatment that is regularly used because physicians have no other choice because to do so would eliminate the requirements for completing any pediatric research.

FDA agrees that just because a certain treatment is consistent with sound medical practice does not mean that it is the standard of care. FDA has stated that whether a medical specialty society that is represented in or recognized by the Council of Medical Specialty Societies (or is a subspecialty of such society) or is recognized by the American Osteopathic Association has found that a new use is consistent with sound medical practice will be considered as evidence that it is the standard of care. Moreover, just because an unapproved use of a drug or device is the standard of care, does not mean that it is automatically exempt from the requirement to conduct the study needed to submit a supplemental application.

79. Several comments noted that it is almost inconceivable that the study of a new use for children could be viewed as unethical.

FDA will make this determination on a case-by-case basis.

80. Several comments argued for making the exemption process public. One comment said that all information should be made public as soon as a manufacturer requests an exemption and that if an exemption is granted all information should remain in the public domain so that interested parties will be able to play a role in keeping FDA informed as to when it should be revoked. Another suggested that prior to granting any exemption, FDA should hold a meeting of the

appropriate advisory committee so that the public has the opportunity to review and comment upon the request.

As set forth previously, FDA declines to adopt a notice and comment process for considering exemption requests. The information will be made available to the public consistent with FOIA and FDA's regulations. FDA has the option of consulting advisory committees about exemption requests, when appropriate.

4. Subpart D—FDA Action on Submissions, Requests, and Applications

a. Agency action on a submission (§ 99.301). Proposed § 99.301 described the range of FDA's actions when it receives a submission. For example, under the proposal, FDA could determine that a manufacturer's submission does not comply with the regulatory requirements, request additional information or documents to assist the agency in determining whether the information to be disseminated complies with applicable requirements, or determine that the information fails to provide data, analyses, or other written matter that is objective and balanced. The proposal also described FDA actions in response to a manufacturer's submission when the manufacturer is committing to submit a supplement on completed studies or is agreeing to conduct the necessary studies and then submit a supplement.

81. Proposed § 99.301(a) provided that, within 60 days, FDA may determine that a submission does not comply with the requirements of the proposal or that it needs more information. A number of comments objected to the proposal because they believed that FDA would use it to extend the 60-day time period. The concern was that FDA would, on day 59, advise a manufacturer that their submission was not complete and therefore the 60-day time period had not begun. The comments said that Congress meant for FDA to give a final answer within the 60-day time period. Some comments argued that FDA should let manufacturers know if their submission is complete within a short period of time, e.g., within 15 days of receiving the submission.

In response to these comments, FDA has eliminated proposed § 99.301(a)(2) so that manufacturers will have a final decision within 60 days. Within the 60-day period, FDA will either

notify a manufacturer that it has not met the requirements set forth in the law or allow the dissemination to go forward. FDA is not adopting the comment's suggestion that it advise sponsors as to whether their submissions are complete within a certain number of days (e.g., 15). The 60-day statutory timeframe is too short for the agency to make a commitment to provide such advice.

82. One comment stated that FDA should be required to notify the manufacturer promptly if it approves a submission in less than 60 days.

There is no requirement in the statute that FDA notify a manufacturer unless it intends to stop the dissemination of information under this part. Therefore, FDA is not revising the regulation as suggested. The agency will, however, make an effort to notify manufacturers promptly if it approves a submission in less than 60 days.

83. One comment requested that FDA change the ''may'' in proposed § 99.301(a) to ''shall'' and to clarify that a sponsor may begin to disseminate material if it has not heard from FDA within 60 days. Another comment suggested that FDA clarify § 99.301 to indicate that FDA will review an IND or IDE and will notify the manufacturer of the IND or IDE approval and that, until such notification, the manufacturer cannot disseminate the information.

FDA declines to change the ''may'' to ''shall'' in § 99.301(a). FDA is not required to do any of the things listed in § 99.301(a), and so use of the word ''shall'' would be inappropriate. Moreover, it is not true that a manufacturer may, in every circumstance, begin dissemination if it has not heard from FDA within 60 days. Under section 554(c) of the act, a manufacturer that has certified that it will conduct the studies needed to submit a supplement and that has submitted a proposed protocol and schedule for conducting such studies cannot disseminate unless the Secretary has determined that the proposed protocol is adequate and that the schedule for completing the studies is reasonable. Nevertheless, FDA has revised § 99.301(b) to state clearly that the agency will make a positive or negative determination on the manufacturer's protocols (and, where appropriate, its schedules) within 60 days after receiving a submission under part 99.

84. Proposed § 99.301(a)(3) (now redesignated as § 99.301(a)(2)) provided that FDA shall provide a manufacturer notice and an opportunity for a meeting regarding the agency's determination that the information submitted is not objective and balanced, and requires additional information. One comment suggested that there should be a specific timeline for when such a meeting would occur.

The statute does not require that FDA set a timeline for such a meeting. Nevertheless, FDA will provide for such an opportunity as soon as is mutually convenient for FDA and the manufacturer. In any event, the meeting will take place within the 60-day period. Furthermore, should FDA determine that additional articles are necessary to provide objectivity and balance, the agency will apply the same standards for scientific soundness to those additional articles.

85. Proposed § 99.301(a)(4) (now redesignated as § 99.301(a)(3)) provided that within 60 days of receiving a manufacturer's submission, FDA may require the manufacturer to maintain records that will identify individual recipients of the information that is to be disseminated.

Some comments supported FDA's not requiring individualized recordkeeping in all situations. Others, however, thought it should be invoked in all situations and still others thought that ever requiring it was too burdensome. One comment argued that the proposed standard for individual recordkeeping was too vague and suggested that FDA make such a request ''only in rare circumstances, when warranted because of special safety considerations associated with a new use.'' One comment argued that FDA should provide notice and an opportunity to meet in the event that it requires a company to maintain records identifying individual recipients.

Section 553(b) of the act (21 U.S.C. 360aaa-2(b)) expressly requires a manufacturer to keep records that the manufacturer may use if it is required to take corrective action. Section 553(b) of the act also states that, ''Such records, at the Secretary's discretion, may identify the recipient of information provided * * * or the categories of such recipients.'' FDA does not believe that it would be appropriate to require individual recordkeeping in all circumstances. Similarly, FDA does not believe that it would be appropriate to require recordkeeping of categories of recipients

in all circumstances. FDA agrees, however, that it should better define the standard for individual recordkeeping and will adopt, with slight modifications, the standard suggested by the comments. Section 99.301(a)(3) provides for individual recordkeeping when warranted because of special safety considerations associated with the new use. FDA did not adopt the ''only in rare circumstances'' language because although it expects to require this in limited circumstances, it does not yet have experience implementing this provision and nothing in the statute or legislative history indicates that Congress intended it to be rare.

86. One comment was concerned that because the agency has to review all submissions within 60 days, sometimes the timeframe will expire and allow information dissemination or exemptions to happen without agency review and thus patients could be harmed before FDA has time to terminate a deemed approval. This comment encouraged the agency to provide information to health care providers on the process by which the review will occur.

FDA recognizes that the act would allow information to be disseminated without agency review. The agency is committed to reviewing all of this information so that inappropriate information does not get disseminated.

87. Proposed § 99.301(b) required FDA to notify the manufacturer if the agency determines that its protocol and schedule for conducting studies are adequate and reasonable. Until FDA provides such notification, dissemination cannot begin. One comment noted that it was not the intent of Congress that the 60-day timeframe be delayed as a result of ongoing IND/IDE negotiations.

The statute provides that a manufacturer who submits a protocol and proposed schedule for conducting the studies needed to submit a supplement, cannot begin to disseminate until FDA determines that they are adequate. (See section 554(c)(1) of the act.) However, as stated earlier, FDA has revised § 99.301(b) to state that the agency will make a positive or negative determination on the manufacturer's protocols (and, where appropriate, its schedules) within 60 days after receiving a submission under 21 CFR part 99.

88. Proposed § 99.301(b) described FDA action on a manufacturer's proposed protocols and schedules for completing studies. One comment said that the rule should clarify which functional groups within FDA will be responsible for the review of protocols and studies and provide for a timeline for such review.

FDA has stated previously that clinical information, including protocols, that is submitted under this part will be reviewed by the appropriate review divisions. It is not necessary for the rule to detail FDA's internal procedure. FDA will review such protocols and schedules within 60 days. Section 99.301(b) includes that timeframe.

89. Under proposed § 99.301(b)(2), if a manufacturer has completed studies that it believes would be an adequate basis for the submission of a supplemental application for the new use and has certified that it will submit such supplement within 6 months, FDA would conduct a preliminary review of the study reports to determine whether the studies are potentially adequate to support the filing of a supplemental application for the new use. If FDA determines that the study reports are inadequate to support the filing of a supplemental application for the new use or are not complete, FDA will notify the manufacturer and the manufacturer shall not disseminate the new use information under this subpart. One comment argued that FDA should not be allowed to take a ''sneak peek'' at preliminary clinical trial data prior to its submission in a supplemental application.

Section 99.201(a)(4)(i) requires manufacturers that have completed studies that they believe would be an adequate basis for the submission of a supplemental application for the new use and have certified that it will submit such supplement within 6 months to submit the protocols for those studies. FDA, will, as in the case of the 36-month certification, review those protocols to determine whether they are adequate. The final rule has been revised to indicate that FDA will review the protocols submitted and not the study reports. However, this does not in any way affect the agency's ability to determine, based on information it has, including information about

clinical trials, that the information a manufacturer seeks to disseminate is false or misleading or would pose a significant risk to public health.

b. Extension of time for completing planned studies (§ 99.303). Proposed § 99.303 described FDA's ability to: (1) On its own initiative, allow a manufacturer more than 36 months to submit a supplemental application, based on the review of the protocols(s) and planned schedule; or (2) grant a manufacturer's request to extend the 36-month period (for up to 24 months). Proposed § 99.303(a) described FDA's ability to determine, on its own initiative and before any studies have begun, that a manufacturer needs more than 36 months to complete the studies needed for submission of a supplemental application and to submit such application. Proposed § 99.303(b) and (c) described FDA's ability, after such studies have begun and the sponsor has submitted a request, to grant an extension of the time to submit a supplement by up to 24 months. FDA would grant such an extension if the manufacturer makes a request for an extension in writing and FDA determines that the manufacturer has acted with due diligence to conduct the studies needed for the submission of a supplemental application for a new use and to submit such a supplemental application, but still needs more time.

90. The comments to this provision indicated that there was some confusion regarding these two different procedures. Several comments asked FDA to more clearly set out the two procedures contemplated by the statute. Several comments asked FDA to make clear that the 24-month limitation applies only to an extension request made after a study has begun. One comment suggested that there could be more than one 24-month extension.

FDA has revised this section to make clear that there are two different types of extensions. The first extension (in § 99.303 (a)) relates to FDA's ability to determine, with or without a request from the manufacturer, that 36 months is not enough time to complete a study of the new use and submit a supplemental application. This would occur before any studies are begun, either before the submission is made or at the time of the submission. There is no limit on how much time FDA may give a manufacturer under this subsection.

The second type of extension (described in revised § 99.303(b)) relates to FDA's ability to grant a manufacturer's request for an extension after a study has begun because, even though it appeared that 36 months would be sufficient and the manufacturer has acted with due diligence, the manufacturer has run into problems and needs more time. This type of extension is limited to 24 months and the statute does not provide that FDA can give more than one 24-month extension.

c. Exemption from the requirement to file a supplemental application (§ 99.305). Proposed § 99.305 described FDA action on a request for an exemption from the requirement to submit a supplemental application and the criteria to be considered in deciding whether to grant a request for an exemption, either because it would be economically prohibitive to conduct the studies needed for a supplemental application or it would be unethical to conduct the clinical studies needed to approve the new use.

91. Proposed § 99.305(a)(1) states that FDA must act on an application for an exemption within 60 days of receipt or it will be deemed approved. However, under proposed § 99.305(a)(2), FDA could, at any time, terminate such deemed approval if it determines that the requirements for granting an exemption have not been met. One comment noted that FDA can terminate such deemed approval only if a manufacturer is disseminating information under section 551 of the act.

Section 554(d)(3)(B) of the act provides that if a manufacturer disseminates information under section 551 of the act under a deemed approval of a request for an exemption, FDA may, at any time, terminate a deemed approval and order the manufacturer to cease disseminating the information under section 553(b)(3) of the act. FDA does not believe that it has to wait for a manufacturer to actually disseminate information in order to terminate the deemed approval.

92. A number of comments suggested that FDA provide a manufacturer an opportunity to meet concerning: (1) FDA's determination that the manufacturer cannot disseminate information under this part; (2) FDA's determination that the manufacturer should maintain records of individual

recipients; (3) FDA's determination of a company's request for an extension of time to complete the necessary studies and submit a supplement; (4) FDA's denial of an exemption.

Section 401 of FDAMA directed FDA to provide manufacturers an opportunity to meet regarding a determination that the information to be disseminated is not balanced and objective and regarding the cessation of information dissemination in certain circumstances. The statute does not direct FDA to meet in the circumstances described previously. Nevertheless, as always, FDA will honor requests for meetings to the fullest extent feasible. Given the short timeframes set forth in section 401 of FDAMA, FDA's resource constraints, and the fact that FDA does not know how many submissions it will receive under this part, FDA is not imposing on itself any additional requirements for meetings by making those meetings a part of the regulation.

5. Subpart E—Corrective Actions and Cessation of Dissemination

Subpart E, as proposed, contained provisions describing the corrective actions that FDA could take or order the manufacturer to take, termination of approvals of applications for exemption, and the applicability of labeling, adulteration, and misbranding authority in the event that dissemination failed to comply with section 551 of the act.

93. One comment claimed that proposed subpart E was ''hollow and meaningless'' because Congress did not give FDA the authority to seek civil money penalties against noncomplying manufacturers.

FDA disagrees with the comment's characterization of subpart E and notes that the agency does, indeed, have the authority to seek civil money penalties from any person who violates most requirements of the act pertaining to devices (see section 303(f) of the act (21 U.S.C. 333(f)). Additionally, arguments regarding other civil money penalty authority for violations of these regulations are beyond the scope of this rulemaking.

a. Corrective actions and cessation of dissemination of information (§ 99.401). Proposed § 99.401 authorized FDA to take corrective actions and to order a manufacturer to cease dissemination of information and take corrective action. In general, the proposal would provide

for corrective action or an order to cease dissemination of information based on post dissemination data, information disseminated by the manufacturer, or the manufacturer's supplemental application for the new use (or its failure to submit or to complete the studies necessary for the supplemental application). Proposed § 99.401 also described the procedures to be observed, such as consultation with the manufacturer, notice regarding FDA's intent to issue an order to cease dissemination, and opportunities for a meeting, and described when a manufacturer shall cease disseminating information in the event of its noncompliance with the regulations.

94. Several comments would revise proposed § 99.401 to give manufacturers a mechanism for appealing the agency's decision to require corrective action. The comments would either amend the rule to refer to the dispute resolution provision at section 562 of the act (21 U.S.C. 360bbb-1), the regulations for internal agency review of decisions (§ 10.75 (21 CFR 10.75)), or other appeals processes.

FDA declines to revise the rule to refer to statutory or regulatory appeals mechanisms. Such appeals mechanisms are available regardless of whether § 99.401 refers to them or not, and it would be both impractical and unnecessary to list all possible statutory and regulatory appeals mechanisms in § 99.401. Moreover, such a list would either become obsolete or useless if any statutory or regulatory citations for the appeals mechanisms changed or would require FDA to monitor constantly all cross-references without any appreciable benefit.

95. Several comments would amend § 99.401 to permit manufacturers to continue disseminating information pending the outcome of any appeal except where a significant safety issue or public health concern exists. In contrast, one comment said that a manufacturer should cease disseminating information while it and FDA are resolving any outstanding issues. FDA declines to revise the rule to allow manufacturers to continue disseminating information pending the outcome of any appeal. In general, section 555 of the act (21 U.S.C. 360aaa-4) authorizes the agency to order a manufacturer to cease dissemination of information on the unapproved/new use; it does not require the agency to stay or defer the effectiveness of such an order pending

any appeal by the manufacturer. This outcome is consistent with the appeals or dispute resolution provisions cited by the comments (section 562 of the act and § 10.75), as well as other regulatory mechanisms for requesting reconsideration (see, e.g., 21 CFR 10.33 (administrative reconsideration of action) and 21 CFR 10.35 (administrative stay of action)); none of these mechanisms results in an automatic stay of agency action while the agency reconsiders its decision or considers an appeal.

96. One comment suggested that FDA define ''appropriate corrective action.'' The comment would amend the rule to give examples of corrective action and to describe the circumstances under which specific corrective actions might apply.

By using the term ''appropriate corrective action,'' FDA meant to give itself the flexibility to fashion the corrective action to remedy the underlying problem or deficiency. As stated in the preamble to the proposed rule, these actions include, but are not limited to, ordering the manufacturer to send ''Dear Doctor'' letters, to publish corrective advertising, to include warning labels on the product, or to include warnings or otherwise revise the product labeling (63 FR 31143 at 31151). FDA declines to define ''appropriate corrective action'' or to give examples and to specify when it might order a manufacturer to take a particular corrective action. The agency's regulatory experience indicates that regulations containing lists or examples often are misconstrued as providing an exclusive list (thereby resulting in unnecessary disputes as to whether a particular corrective action is within the regulation or whether the manufacturer's action is even capable of being addressed by the agency) and that regulations that describe specific responses to specific situations can deprive the agency of the flexibility to tailor a corrective action to fit a particular situation. Nevertheless, FDA would note that it expects that ''Dear Doctor'' letters and/or corrective advertising would be used much more often than the addition of warning statements or product labeling, which are likely to be used in the more extreme cases.

97. Proposed § 99.401(a) permitted FDA to take appropriate action to protect the public health, including ordering a manufacturer to cease dissemination and take corrective action, if FDA

determines, based on data received after the dissemination has begun, that the new use that is the subject of the disseminated information may not be effective or may pose a significant risk to public health. The provision required FDA to consult with the manufacturer before taking any such action.

One comment disagreed that FDA should have any obligation to consult a manufacturer before ordering the manufacturer to cease disseminating information on an unapproved/new use.

Section 555(a)(1) of the act, regarding corrective actions following the receipt of data after a manufacturer has begun disseminating information, expressly states that the agency, ''after consultation with the manufacturer,'' shall take ''such action regarding the dissemination of the information as [the agency] determines to be appropriate for the protection of the public health, which may include ordering that the manufacturer to cease dissemination of the information.'' Thus, with respect to corrective actions based on post-dissemination data, the act requires FDA to consult the manufacturer before taking any action, and § 99.401(a) correctly reflects this statutory requirement.

98. FDA revised § 99.401(c)(3) and (c)(4), by changing the references to § 99.303 from paragraphs (a) or (c) to paragraphs (a) or (b). This change was needed to correct an error and to reflect the changes made to § 99.303, which were previously discussed.

99. Proposed § 99.401(b) discussed FDA's ability to order cessation of dissemination or corrective action because the information being disseminated by a manufacturer does not comply with part 99. Proposed § 99.401(b)(1) directed FDA to give a manufacturer the opportunity to bring itself into compliance if the manufacturer's noncompliance constituted a minor violation. Proposed § 99.401(b)(2) permitted FDA to order the manufacturer to cease dissemination of information after providing notice to the manufacturer and an opportunity for a meeting.

One comment would revise § 99.401(b)(2) to specify a timeframe for a meeting, but did not explain why such specificity would be beneficial.

FDA declines to revise the rule as suggested by the comment. Because FDA cannot require a manufacturer to cease dissemination until it has provided an opportunity for a meeting, it has an incentive to schedule such meetings at the earliest possible time, particularly when the new use at issue raises significant safety concerns. By not specifying a timeframe for a meeting, the regulation provides the appropriate flexibility to schedule meetings.

100. One comment said that FDA should afford manufacturers an opportunity to resolve outstanding issues before taking any corrective action to avoid burdensome and erroneous corrective action.

Section 555(b)(1) of the act requires FDA to delay issuing an order to provide a manufacturer an opportunity to correct a minor violation before ordering such manufacturer to cease dissemination. Section 99.401(b) provides that opportunity. Moreover, FDA will always consider whether and when corrective action is appropriate.

101. Proposed § 99.401(c) described FDA actions based on a manufacturer's supplemental application. For example, under proposed § 99.401(c)(1), FDA could order a manufacturer to cease dissemination and to take corrective action if the agency determined that the supplemental application does not contain adequate information for approval of the new use.

One comment said that FDA should not automatically require a manufacturer to cease dissemination if FDA does not approve a supplemental application for the unapproved/new use because it fails to establish effectiveness. The comment said corrective action should be reserved for situations in which "some significant public health concern is identified that would be materially addressed by such corrective action."

FDA declines to revise § 99.401(c) to limit corrective actions as suggested by the comment. If FDA, based on the supplemental application submitted by the manufacturer, determines that the drug or device is not effective for that use, it could be contrary to the interests of public health to allow the manufacturer to continue disseminating information on that use. Section 555(b)(2) of the act contemplates such a result by stating that the agency may order a manufacturer

to cease dissemination if the agency determines that the supplemental application does not contain adequate information for approval of the new use.

Furthermore, one should note that both section 555(b)(2) of the act and § 99.401(c) give FDA discretion in issuing an order to cease dissemination of information on the unapproved/new use if FDA does not approve the supplemental application. Thus, contrary to the comment's assertion, an order to cease dissemination under such circumstances is not ''automatic.''

102. One comment said that if FDA does not approve a supplemental application because the studies failed to demonstrate efficacy, the manufacturer should advise health care practitioners who previously received information on the unapproved/new use.

Requiring a manufacturer to notify recipients or categories of recipients that a drug or device is not effective for the unapproved/new use would be within the range of corrective actions that FDA may take. Section 553(b) of the act contemplates such a result by requiring manufacturers to keep records of categories of recipients or individual recipients of the disseminated information and to use such records if the manufacturer is required to take corrective action. Thus, corrective actions, in § 99.401, are not confined to orders to cease dissemination of information on an unapproved/new use.

103. One comment sought clarification as to when FDA may determine that a supplemental application does not contain adequate information for approval of the new use. The comment suggested that proposed § 99.401(c)(1) could be interpreted as applying even if FDA requested additional information or clarification of a supplemental application. The comment stated that dissemination of information on an unapproved/new use should cease only when FDA determines that the supplemental application is not approvable.

Section 555(b)(2) of the act permits FDA to order a manufacturer to cease dissemination if FDA determines that a supplemental application submitted by such manufacturer (for the new use) does not contain adequate information for approval of the new use. Section 99.401(c)(1) tracks this language. FDA agrees that a decision to seek additional data or clarification regarding a

supplemental application would generally not constitute a determination that the supplement does not contain adequate information for approval of the new use. However, there may be circumstances in which it is appropriate for the agency to order a manufacturer to cease dissemination of information when additional data is required. Accordingly, FDA will make these determinations on a case-by-case basis.

104. Proposed § 99.401(c)(2) permitted FDA to order a manufacturer to cease dissemination if the manufacturer had certified that it would submit a supplemental application within 6 months, and the manufacturer failed to submit a supplemental application within 6 months.

One comment said FDA should not seek corrective action for a manufacturer's failure to submit a supplemental application within 6 months if there is ''good cause'' for the delay. The comment said that FDA should meet with a manufacturer to determine if there is good cause for the delay before automatically requiring corrective action and that manufacturers should notify FDA as soon as possible if they will not meet any deadline.

FDA declines to revise the rule as requested by the comment. Section 99.401(c)(2) does not require any specific corrective action in the event that the manufacturer fails to submit a supplemental application on time. Instead, it gives FDA the discretion to order the manufacturer to cease dissemination of information and to take corrective action. FDA will consider, among other things, the reasons for a manufacturer's inability to submit a supplemental application on time when deciding what type of corrective action to take or whether any corrective action is needed.

Thus, while FDA would appreciate any advance notice from manufacturers who believe that they will be unable to submit a supplemental application on time and will meet with manufacturers as time and resources permit, given the agency's discretion regarding corrective actions in § 99.401(c)(2), revising the rule to require such meetings is unnecessary.

105. Proposed § 99.401(d) considered an order to cease dissemination of information to be effective upon the date of issuance unless otherwise stated by FDA.

One comment said it would be more efficient if an order to cease dissemination of information were effective upon date of receipt by the manufacturer. The comment explained that a manufacturer may be unaware when FDA issues an order to cease dissemination of information, so the order should be effective when the manufacturer receives it. The comment also stated that it would be unlikely that a manufacturer could stop dissemination of information throughout the United States on the same day it receives an order to cease dissemination. Consequently, the comment would revise the rule to give manufacturers some time (the comment suggested 60 days) in which to comply with the order.

FDA agrees, in part, with the comment and has revised § 99.401(d) to make an order to cease dissemination of information effective upon receipt by the manufacturer, unless otherwise indicated in the order. The agency does not agree that manufacturers should have a specified amount of time after receipt to comply with an order. A manufacturer is expected to comply immediately. If the manufacturer is unable to comply immediately, it should notify FDA, and FDA will evaluate the situation on a case-by-case basis.

106. Proposed § 99.401(e) required a manufacturer to cease dissemination if it fails to comply with the regulations pertaining to dissemination of information on unapproved/new uses. This would include discontinuation, termination, and a failure to conduct with due diligence clinical studies. The proposal also required the manufacturer to notify FDA if it ceases dissemination under § 99.401(e).

One comment would revise the rule to require a manufacturer to notify FDA of any failure to comply as soon as the manufacturer realizes the failure and ceases dissemination. The comment also would require the manufacturer to notify FDA immediately if the manufacturer ceases dissemination. Section 99.401(e) already requires a manufacturer to notify FDA if it ceases dissemination.

FDA agrees that the agency should be notified immediately and has revised § 99.401(e) accordingly.

b. Termination of approvals of applications for exemption (§ 99.403). Under the act, if FDA fails to act within 60 days on an application for an exemption from the requirement to file a supplemental application, the application is deemed approved. Proposed § 99.403 allowed FDA to terminate the deemed approval of an application for an exemption if FDA determines that the manufacturer has failed to meet the requirements for granting an exemption. In addition, the agency may order the manufacturer to cease disseminating information about the new use and, if appropriate, to take corrective action.

107. One comment would revise § 99.403(a)(3) to apply if FDA determines that it would be economically *and* ethically possible to conduct the studies needed for a supplement rather than economically *or* ethically possible to conduct such studies.

FDA agrees and has revised the rule accordingly.

108. One comment requested that FDA provide notice and an opportunity to meet when FDA terminates approval of an application for an exemption.

Section 99.403(c), (d), and (e) provide for notice to the manufacturer, and § 99.403(d) also mentions consultation between FDA and the manufacturer if FDA determines that the manufacturer no longer meets the requirements for an exemption on the basis that it is economically prohibitive or unethical to conduct the studies needed to support a supplemental application for the new use. Thus, no further change to the rule is necessary.

c. Applicability of labeling, adulteration, and misbranding authority (§ 99.405). Proposed § 99.405 provided that the dissemination of information about a new use could constitute labeling, evidence of a new intended use, adulteration or misbranding of the product if it fails to comply with the requirements in section 551 of the act and the requirements of this part.

109. One comment claimed that proposed § 99.405 was too broad and exceeded the statute by considering a failure to comply with part 99 to constitute labeling, evidence of a new intended use, adulteration, or misbranding of a drug or device. The comment acknowledged that labeling that is false or misleading renders a drug misbranded and that each introduction of the drug into

interstate commerce constitutes a separate prohibited act under section 301 of the act (21 U.S.C. 331). The comment further acknowledged that FDA can pursue various enforcement actions, such as seizures, injunctions, and criminal penalties, for each prohibited act. However, the comment argued that a failure to comply with part 99 should be a single violation rather than a violation for each product sold and that if a manufacturer tries to follow part 99, the act prescribes specific enforcement consequences, such as corrective action, before FDA resorts to other sanctions.

FDA disagrees with this comment. Although section 401 of FDAMA provided FDA additional enforcement tools for violative dissemination of off-label information, it did not in any way eliminate or limit FDA's ability to use its already existing enforcement mechanisms.

6. Subpart F—Recordkeeping and Reports

Recordkeeping and reports (§ 99.501). Proposed § 99.501 required a manufacturer that disseminates information under part 99 to maintain records sufficient to allow it to take corrective action that is required by FDA and described some of the records to be kept. The proposal gave manufacturers the option of maintaining records that identify recipients of the disseminated information by name or by category, but would require manufacturers who choose to identify recipients by category to ensure that any corrective action FDA requires will be sufficiently conspicuous so as to reach the individuals who have received the information about the new use. The proposal also permitted FDA to require manufacturers to keep records identifying recipients by name and required a manufacturer to keep records for 3 years after it has ceased disseminating the information on an unapproved or new use and to make the records available to FDA for inspection and copying.

110. One comment suggested that FDA permit manufacturers to submit reports via the Internet. The comment said that this would reduce paperwork burdens and provide a continuous source of current information.

FDA currently receives certain submissions from industry in electronic form and encourages increased utilization of this means. Initiatives are underway to formalize a process for electronic submission.

111. Several comments focused on proposed § 99.501(a)(1)(i), which required records to identify, by name, the persons receiving the disseminated information. This provision would apply if the manufacturer did not keep records identifying recipients by category or if FDA required the manufacturer to keep records identifying recipients by name. One comment supported the provision as written. Several comments would amend the rule to require manufacturers to keep records identifying recipients by name in all cases. These comments explained that requiring manufacturers to maintain records of specific recipients would help ensure timely action or notification if the new use is ineffective or presents a significant risk to the public health. The comments said such records also would help ensure that the manufacturer disseminated the information to the appropriate recipients. Two comments suggested requiring manufacturers to keep records of health professionals by name, health plans, and pharmacies that receive information in cases of a recall.

In contrast, several comments objected to ever requiring manufacturers to identify recipients by name. Some comments acknowledged that section 553(b) of the act ''technically'' gives FDA the discretion to require such records, but nevertheless said the provision was ''unnecessary'' or ''unduly burdensome.'' These comments would delete the requirement and only require manufacturers to maintain records identifying recipients by category.

FDA declines to revise the rule as suggested by the comments. Section 553(b) of the act expressly requires a manufacturer to keep records that the manufacturer may use if it is required to take corrective action. Section 553(b) of the act also states that, ''Such records, at the Secretary's discretion, may identify the recipient of the information provided * * * or the categories of such recipients.'' To require manufacturers to keep records identifying the recipients in all cases, or in no cases, as suggested by the comments, would be contrary to the express terms in section

553(b) of the act. As previously discussed, however, FDA has better defined the standard for individual recordkeeping. Section 99.301(a)(3) of the final rule provides for individual recordkeeping when warranted because of special safety considerations associated with the new use.

112. One comment claimed that proposed § 99.501(a)(1)(i) exceeded the statutory requirement. The comment said that if FDA requires a manufacturer to maintain records identifying recipients by category, then if corrective action is later required, FDA should not expect manufacturers to generate lists of individual recipients that are to receive such corrective action.

The comment misinterprets the rule. Under § 99.301(a)(3), when FDA reviews a manufacturer's submission, the agency would determine whether records identifying individual recipients must be kept. FDA would impose such a requirement in limited circumstances before the manufacturer disseminates any information on the unapproved/new use. Section 99.501(a)(1)(i) does not provide a new mechanism for requiring manufacturers to keep records identifying individual recipients nor does it contemplate requiring manufacturers not previously required to identify individual recipients to generate such records if corrective action becomes necessary.

113. Several comments discussed the semiannual submissions to FDA under proposed § 99.501(b). Several comments objected to proposed § 99.501(b)(3) and (b)(4), which required a notice and summary of any additional clinical research or other data relating to the safety or effectiveness of the new use and periodic progress reports on the manufacturer's studies. The comments stated that such reporting requirements would duplicate information that FDA already receives under existing reporting requirements for IND's and NDA's. One comment objected to the semiannual frequency of the reports. Another argued that FDA failed to set forth ''limits on the responsibilities'' of manufacturers ''as the Secretary deems appropriate'' regarding additional information that must be submitted. Finally, one comment asked FDA to acknowledge that these reports are exempt from disclosure under FOIA.

Section 99.501(b)(3) and (b)(4) reflect the statutory requirement at sections 555(a)(2) and 554(c)(2) of the act respectively. Section 555(a)(2) of the act states that, after a manufacturer disseminates information, the manufacturer shall submit ''a notification of any additional knowledge of the manufacturer on clinical research or other data that relate to the safety or effectiveness of the new use involved.'' Section 554(c)(2) of the act requires a manufacturer to submit periodic progress reports on its clinical studies. FDA drafted the proposed rule to have these periodic progress reports submitted on a semiannual basis in order to coincide with the reporting frequency for the lists of articles and categories of providers required by section 553(a) of the act. This would be more convenient for both manufacturers and the agency to have the reports and lists submitted at the same time. Thus, FDA did not intend to require duplicate reporting of information that is already submitted to the agency under other FDA regulations nor did FDA intend to make the submission of such reports burdensome.

To the extent that the information described in § 99.501(b)(3) and (b)(4) is already submitted to FDA as part of the routine reporting for an application for investigational use or for a marketing application, manufacturers may comply with § 99.501(b)(3) and (b)(4) by making a cross-reference to the relevant application for investigational use or for a marketing application. Thus, a manufacturer does not have to duplicate information that it has already submitted to FDA. Moreover, FDA did set limits on the manufacturers' responsibilities by requiring that the information be reported on a semiannual basis. Finally, as stated earlier, public disclosure of information submitted under this rule is dictated by the FOIA and FDA's regulations.

114. One comment sought clarification that a manufacturer must submit any additional article or publication to FDA before it can be disseminated. The concern was that manufacturers would interpret the semiannual filing requirement as sufficient once a manufacturer has received approval to disseminate information about a particular use.

The statute and regulation make clear that the manufacturer has to come to FDA before beginning to disseminate a journal article or reference publication that has not previously been

submitted to FDA. In other words, once FDA has approved or passed on a specific journal article or reference text, the manufacturer can disseminate it to as many qualified recipients as it chooses, as long as the manufacturer continues to meet the requirements of this part. However, even if FDA has approved or passed on one journal article or reference publication for a new use, the manufacturer may not disseminate additional/different journal articles or reference publications for that same use without making a separate submission.

115. If a manufacturer received an exemption from the requirement to submit a supplemental application, proposed § 99.501(b)(5) would require the manufacturer to submit any new or additional information that relates to whether the manufacturer continues to meet the requirements for the exemption. One comment objected to this requirement, saying that it would need extensive market data to continue justifying the need for an exemption on economic grounds and that the cost of generating such information would itself be economically prohibitive.

FDA disagrees that it would be economically prohibitive to comply with this requirement. The regulation requires manufacturers only to provide new or additional information.

116. Proposed § 99.501(c) required a manufacturer to maintain a copy of all information, lists, records, and reports required or disseminated under part 99 for 3 years after it has ceased dissemination of such information and to make such documents available to FDA for inspection and copying. One comment requested clarification of this provision. The comment explained that if FDA approves the manufacturer's supplemental application, then the manufacturer would no longer be disseminating information on an unapproved/new use and would not be subject to part 99. Instead, any postapproval dissemination of information would be on an approved use and, therefore, would not be subject to the recordkeeping requirement in § 99.501(c).

The comment's interpretation of § 99.501(c) is correct. If FDA approves the manufacturer's supplemental application, the use is then ''approved'' and dissemination of information on the approved use would be outside the scope of part 99. However, documents relating to the dissemination of information before approval would remain subject to § 99.501.

7. Conforming Amendment to 21 CFR Part 16

The proposed rule would amend 21 CFR 16.1(b)(2) to add the due diligence determination under proposed § 99.401(c) to the list of regulatory actions that may be the subject of a part 16 hearing.

FDA received no comments on this provision and has finalized it without change.

IV. Analysis of Impacts

FDA has examined the impacts of the final rule under Executive Order 12866 and the Regulatory Flexibility Act (5 U.S.C. 601–612). Executive Order 12866 directs agencies to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages). Under the Regulatory Flexibility Act, unless an agency certifies that a rule will not have a significant economic impact on a substantial number of small entities, the agency must analyze regulatory options that would minimize the impact of the rule on small entities. Title II of the Unfunded Mandates Reform Act (Pub. L. 104–4) (in section 202) requires that agencies prepare an assessment of anticipated costs and benefits before proposing any rule that may result in an expenditure in any 1 year by State, local, and tribal governments, in the aggregate, or by the private sector, of $100 million or more (adjusted annually for inflation).

The agency has reviewed this rule and has determined that it is consistent with the regulatory philosophy and principles identified in Executive Order 12866, and in these two statutes. Although this rule is not an economically significant regulatory action, it is still a significant regulatory action as defined by the Executive Order due to the novel policy issues it raises. With respect to the Regulatory Flexibility Act, the agency certifies that the rule will not have a significant economic impact on a substantial number of small entities. Because the final rule does not impose any mandates on State, local, or tribal governments, or the private sector that will result in a

1-year expenditure of $100 million or more, FDA is not required to perform a cost-benefit analysis under the Unfunded Mandates Reform Act.

The rule implements section 401 of FDAMA by describing the new use information that a manufacturer may disseminate and by setting forth procedures that manufacturers must follow before disseminating information on the new use. The benefits of the rule will derive from the public health gains associated with the earlier dissemination of objective, balanced, and accurate information on important unapproved uses of approved products. In addition, the rule may encourage new studies or the collection of evidence about these new uses.

The costs of the rule are modest. A firm would typically conduct clinical studies in support of a supplemental application for a new use only if the firm believed that the added revenues associated with the new indication would exceed the costs of the supporting studies. Because this rule will accelerate the receipt of these revenues, it is possible that some new use supplemental applications that would not have been economically justified in the absence of this rule, will now be submitted. No comments on the proposed rule attempted to project the magnitude of this incentive and FDA similarly could not estimate the number or cost of the additional clinical studies that might accompany these applications. The agency notes, however, that they would be undertaken voluntarily by the affected firms in the expectation that they would increase company profitability.

Manufacturers choosing not to disseminate new use information will incur no costs. Firms voluntarily choosing to disseminate new use information will experience added paperwork costs for each submission to the agency, but gain sales revenues from the information dissemination. FDA cannot make a precise estimate of the number of submissions that will be filed, but as explained in section V of this document, the agency tentatively forecasts that it will receive approximately 300 submissions each year from manufacturers for the purpose of disseminating new use information. FDA also estimates that the statutory and regulatory paperwork burdens associated with these submissions might total almost 52,000 hours, at an average labor cost of

$35 per hour.[1] Thus, the total cost of the added paperwork is estimated to cost industry approximately $1.8 million per year. FDA received no public comments that specifically addressed its paperwork estimates.

The final rule should not have an adverse impact on any manufacturer. One comment asserted that the agency's definition of economically prohibitive implies that some manufacturers will disseminate information despite a resulting reduction in net income. The comment further indicated that this reduction in net income requires FDA to undertake additional analysis under the Regulatory Flexibility Act. The agency disagrees with this comment, because the final rule simply makes the dissemination of unapproved use information an option for those firms that find it beneficial to do so. Firms will compare the expected sales revenue from the new dissemination activity to the associated paperwork cost and disseminate the new information only if it increases their profitability. As noted previously, firms choosing not to disseminate new use information will face no increased costs. Because no firm is likely to experience a reduced net income, the rule will not have a significant adverse economic effect on a substantial number of small entities and no further analysis is required under the Regulatory Flexibility Act.

V. Paperwork Reduction Act of 1995

This rule contains information collection requirements that are subject to public comment and review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501–3520). A description of these provisions is given below in this section of the document with an estimate of the annual reporting and recordkeeping burden. Included in the estimate is the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing each collection of information.

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[1] Updated from Eastern Research Group, Inc., "Final Report—Economic Threshold and Regulatory Flexibility Assessment of Proposed Changes to the Current Good Manufacturing Practice Regulations for Manufacturing, Processing, Packaging, or Holding Drugs (21 CFR 210 and 211)," March 13, 1995. Calculation allocates 50 percent of hours to middle management, 25 percent to upper management, and 25 percent to support staff.

FDA had submitted the information collection requirements for the proposed rule to OMB for its review. In its Notice of Office of Management and Budget Action, dated July 30, 1998, OMB stated that it had concerns regarding the burden and utility of the information collection that were to be ''assessed in light of public comments received.'' The terms of OMB clearance further stated that OMB:

> is particularly interested in determining whether the public has comments on the burden and utility of the information required to be included in a submission to FDA, including information submitted to meet the economically prohibitive' exception, and the three year recordkeeping requirement proposed in the rule. FDA shall specifically address any comments received on these and other issues related to the information collection requirements * * *.

The proposed rule provided an opportunity for public comment on the information collection requirements, but FDA received no comments that provided any contrary or different estimates. The agency did receive one comment declaring that the estimated information collection burden for the proposed rule ''may not be an accurate reflection of the actual burden,'' but the comment provided no data or further information that would enable FDA to revise the estimated information collection burden for the final rule.

The agency received several comments that questioned the utility of the information collection requirements. For example, several comments requested changes to the information that would be required to obtain an exemption when a manufacturer felt it would be ''economically prohibitive'' or ''unethical'' to conduct studies necessary to support a supplemental application. These comments generally stated that the proposed rule's criteria were too restrictive. The agency revised the ''economically prohibitive'' criteria in response to the comments and modified the language in the ''unethical'' exemption. These issues are discussed in more detail in the preamble to the final rule.

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The agency did not receive any comments that questioned the utility of the 3-year recordkeeping requirement. One comment sought clarification as to whether the recordkeeping requirement would still apply if FDA approved the supplemental application for the new use, and FDA has addressed that comment in its discussion of the recordkeeping provision.

FDA did, however, simplify the provision concerning the ''economically prohibitive'' exception in response to comments it received. FDA discusses the impact of this revision on the estimated annual reporting burden later in this section.

FDA requested emergency processing of the information collection requirements for this final rule. OMB granted approval to the collection of information and assigned a control number (OMB 0910–0390). The final rule's information collection requirements, therefore, are effective upon (*insert date of publication in the* **Federal Register**). However, the agency is also submitting the information collection requirements for the final rule to OMB for routine processing. Consequently, FDA is providing an opportunity for public comment on the final rule's information collection requirements.

FDA invites comments on: (1) Whether the collection of information is necessary for the proper performance of FDA's functions, including whether the information will have practical utility; (2) the accuracy of FDA's estimate of the burden of the collection of information, including the validity of the methodology and assumptions used; (3) ways to enhance the quality, utility, and clarity of the information to be collected; and (4) ways to minimize the burden of the collection

of information on respondents, including through the use of automated collection techniques, when appropriate, and other forms of information technology.

Title: Dissemination of Treatment Information on Unapproved/New Uses for Marketed Drugs, Biologics, and Devices.

Description: The rule implements sections 551 through 557 of the act (21 U.S.C. 360aaa-360aaa-6) as amended by FDAMA, which requires a manufacturer that intends to disseminate certain treatment information on unapproved uses for a marketed drug, biologic, or device to submit that information to FDA. The rule sets forth the criteria and procedures for making such submissions. Under the rule, a submission would include a certification that the manufacturer has completed clinical studies necessary to submit a supplemental application to FDA for the new use and will submit the supplemental application within 6 months after dissemination of information can begin. If the manufacturer has planned, but not completed, such studies, the submission would include proposed protocols and a schedule for conducting the studies, as well as a certification that the manufacturer will complete the clinical studies and submit a supplemental application no later than 36 months after dissemination of information can begin. The rule also permits manufacturers to request extensions of the time period for completing a study and submitting a supplemental application and to request an exemption from the requirement to submit a supplemental application. The rule prescribes the timeframe within which the manufacturer shall maintain records that would enable it to take corrective action. The rule requires the manufacturer to submit lists pertaining to the disseminated articles and reference publications and the categories of persons (or individuals) receiving the information and to submit a notice and summary of any additional research or data (and a copy of the data) relating to the product's safety or effectiveness for the new use. The rule requires the manufacturer to maintain a copy of the information, lists, records, and reports for 3 years after it has ceased dissemination of the information and to make the documents available to FDA for inspection and copying.

Description of Respondents: All manufacturers (persons and businesses, including small businesses) of drugs, biologics, and device products.

The estimated burden associated with the information collection requirements for this rule is 52,208 hours.

FDA estimates the burden of this collection of information as follows:

TABLE 1.—ESTIMATED ANNUAL REPORTING BURDEN[1]

21 CFR Section	No. of Respondents	Annual Frequency per Response	Total Annual Responses	Hours per Response	Total Hours
99.201(a)(1)	172	1.7	297	40	11,880
99.201(a)(2)	172	1.7	297	24	7,128
99.201(a)(3)	172	1.7	297	1	297
99.201(a)(4)(i)(A)	52	1.7	89	30	2,670
99.201(a)(4)(ii)(A)	52	1.7	89	60	5,340
99.201(a)(5)	52	1.7	89	1	89
99.201(b)	172	1.7	297	0.5	148.5
99.201(c)	172	1.7	297	0.5	148.5
99.203(a)	1	1.7	1	10	10
99.203(b)	1	1.7	1	10	10
99.203(c)	2	1	2	0.5	1
99.205(b)	17	1.8	30	82	2,460
99.501(b)(1)	172	3.4	594	8	4,752
99.501(b)(2)	172	3.4	594	1	594
99.501(b)(3)	172	3.4	594	20	11,880
99.501(b)(4)	2	1.7	3	2	6
99.501(b)(5)	17	1.8	30	41	1,230
Total Hours					48,644

[1] There are no capital costs or operating and maintenance costs associated with this collection of information.

TABLE 2.—ESTIMATED ANNUAL RECORDKEEPING BURDEN[1]

21 CFR Section	No. of Recordkeepers	Annual Frequency per Recordkeeping	Total Annual Records	Hours per Recordkeeper	Total Hours
99.501(a)(1)	172	1.7	297	10	2,970
99.501(a)(2)	172	1.7	297	1	297
99.501(c)	172	1.7	297	1	297
Total Hours					3,564

[1] There are no capital costs or operating and maintenance costs associated with this collection of information.

FDA derived these estimates primarily from existing data on submissions made under supplemental applications and other submissions to the agency, as well as information from industry sources regarding similar or related reporting and recordkeeping burdens.

However, because the final rule revises the "economically prohibitive" exception requirement, FDA has decreased the estimated burden associated with an exemption request under § 99.205(b) and has increased the number of annual responses seeking an exemption. In the preamble to the proposed rule, FDA estimated that 1 percent or approximately 2 of the 172 manufacturers would submit an exemption request. The estimated reporting burden for § 99.205(b), as originally

proposed, was 125 hours per response. This was based on a similar reporting burden for certain submissions under (§ 316.20 (21 CFR 316.20)) even though FDA stated that the actual reporting burden would probably be less because proposed § 99.205(b) was not as extensive as § 316.20. For the final rule, FDA has reduced the estimated reporting burden per response to 82 hours because the revised requirements are not as extensive as those in the proposal and has increased the total number of respondents and annual responses to 17 and 30 respectively (or approximately 10 percent of all respondents and submissions). This results in a total hour burden of 2,460 hours for § 99.205(b). Additionally, FDA has revised § 99.203 to permit manufacturers to request an extension of the 36-month time period for conducting studies and submitting a supplemental application before it makes a submission to FDA. FDA, therefore, has adjusted the information collection tables to reflect this revision.

The estimated increase in the number of exemption requests results in a corresponding decrease in the remaining number of submissions under § 99.201(a)(4)(i)(A), (a)(4)(ii)(A), and (a)(5). FDA assumes that the remaining 267 submissions will be divided equally among § 99.201(a)(4)(i)(A), (a)(4)(ii)(A), and (a)(5) resulting in 89 responses in each provision and approximately 52 respondents per provision. Although FDA has not altered the estimated burden hours per response for § 99.201(a)(4)(i)(A), (a)(4)(ii)(A), and (a)(5), the total burden hours for each of these provisions is reduced due to the smaller number of annual responses.

Additionally, the final rule accounts for the estimated annual reporting and recordkeeping burdens for several provisions (§§ 99.201(a)(1), 99.201(a)(2), 99.203(a), 99.501(a)(1), 99.501(b)(1), 99.501(b)(3), 99.501(b)(5), and 99.501(c)). These provisions were omitted from the Paperwork Reduction Act discussion in the preamble to the proposed rule. The final rule also accounts for the statutory reporting burden associated with § 99.201(a)(4).

The agency has submitted the information collection requirements of this rule to OMB for review. Interested persons are requested to send comments regarding information collection by

(*insert date 60 days after date of publication in the* **Federal Register**), to the Dockets Management Branch (address above).

VI. Environmental Impact

The agency has determined under 21 CFR 25.30(h) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

List of Subjects

21 CFR Part 16

Administrative practice and procedure.

21 CFR Part 99

Administrative practice and procedure, Biologics, Devices, Drugs, Reporting and recordkeeping requirements.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Acting Commissioner of Food and Drugs, 21 CFR chapter I is amended to read as follows:

PART 16—REGULATORY HEARING BEFORE THE FOOD AND DRUG ADMINISTRATION

1. The authority citation for 21 CFR part 16 is revised to read as follows:

Authority: 15 U.S.C. 1451–1461; 21 U.S.C. 141–149, 321–394, 467f, 679, 821, 1034; 28 U.S.C. 2112; 42 U.S.C. 201–262, 263b, 364.

2. Section 16.1 is amended in paragraph (b)(2) by numerically adding an entry for § 99.401(c) to read as follows:

§ 16.1 Scope.

* * * * *

(b) * * *

(2) Regulatory provisions:

* * * * *

§ 99.401(c), relating to a due diligence determination concerning the conduct of studies necessary for a supplemental application for a new use of a drug or device.

* * * * *

3. Part 99 is added to read as follows:

PART 99—DISSEMINATION OF INFORMATION ON UNAPPROVED/NEW USES FOR MARKETED DRUGS, BIOLOGICS, AND DEVICES

Subpart A—General Information

Sec.

Subpart B—Information to be Disseminated

Subpart C—Manufacturer's Submissions, Requests, and Applications

Subpart D—FDA Action on Submissions, Requests, and Applications

Subpart E—Corrective Actions and Cessation of Dissemination

Subpart F—Recordkeeping and Reports

Authority: 21 U.S.C. 321, 331, 351, 352, 355, 360, 360c, 360e, 360aa–360aaa–6, 371, and 374; 42 U.S.C. 262.

Subpart A—General Information

§ 99.1 Scope.

(a) This part applies to the dissemination of information on human drugs, including biologics, and devices where the information to be disseminated:

(1) Concerns the safety, effectiveness, or benefit of a use that is not included in the approved labeling for a drug or device approved by the Food and Drug Administration for marketing or in the statement of intended use for a device cleared by the Food and Drug Administration for marketing; and

(2) Will be disseminated to a health care practitioner, pharmacy benefit manager, health insurance issuer, group health plan, or Federal or State Government agency.

(b) This part does not apply to a manufacturer's dissemination of information that responds to a health care practitioner's unsolicited request.

§ 99.3 Definitions.

(a) *Agency* or *FDA* means the Food and Drug Administration.

(b) For purposes of this part, a *clinical investigation* is an investigation in humans that tests a specific clinical hypothesis.

(c) *Group health plan* means an employee welfare benefit plan (as defined in section 3(1) of the Employee Retirement Income Security Act of 1974 (29 U.S.C. 1002(1))) to the extent that the plan provides medical care (as defined in paragraphs (c)(1) through (c)(3) of this section and including items and services paid for as medical care) to employees or their dependents (as defined under the terms of the plan) directly or through insurance, reimbursement, or otherwise. For purposes of this part, the term *medical care* means:

(1) Amounts paid for the diagnosis, cure, mitigation, treatment, or prevention of disease, or amounts paid for the purpose of affecting any structure or function of the body;

(2) Amounts paid for transportation primarily for and essential to medical care referred to in paragraph (c)(1) of this section; and

(3) Amounts paid for insurance covering medical care referred to in paragraphs (c)(1) and (c)(2) of this section.

(d) *Health care practitioner* means a physician or other individual who is a health care provider and licensed under State law to prescribe drugs or devices.

(e) *Health insurance issuer* means an insurance company, insurance service, or insurance organization (including a health maintenance organization, as defined in paragraph (e)(2) of this section) which is licensed to engage in the business of insurance in a State and which is subject to State law which regulates insurance (within the meaning of section 514(b)(2) of the Employee Retirement Income Security Act of 1974 (29 U.S.C. 1144(b)(2))).

(1) Such term does not include a group health plan.

(2) For purposes of this part, the term *health maintenance organization* means:

(i) A Federally qualified health maintenance organization (as defined in section 1301(a) of the Public Health Service Act (42 U.S.C. 300e(a)));

(ii) An organization recognized under State law as a health maintenance organization; or

(iii) A similar organization regulated under State law for solvency in the same manner and to the same extent as such a health maintenance organization.

(f) *Manufacturer* means a person who manufactures a drug or device or who is licensed by such person to distribute or market the drug or device. For purposes of this part, the term may also include the sponsor of the approved, licensed, or cleared drug or device.

(g) *New use* means a use that is not included in the approved labeling of an approved drug or device, or a use that is not included in the statement of intended use for a cleared device.

(h) *Pharmacy benefit manager* means a person or entity that has, as its principal focus, the implementation of one or more device and/or prescription drug benefit programs.

(i) A *reference publication* is a publication that:

(1) Has not been written, edited, excerpted, or published specifically for, or at the request of, a drug or device manufacturer;

(2) Has not been edited or significantly influenced by such a manufacturer;

(3) Is not solely distributed through such a manufacturer, but is generally available in bookstores or other distribution channels where medical textbooks are sold;

(4) Does not focus on any particular drug or device of a manufacturer that disseminates information under this part and does not have a primary focus on new uses of drugs or devices that are marketed or are under investigation by a manufacturer supporting the dissemination of information; and

(5) Does not present materials that are false or misleading.

(j) *Scientific or medical journal* means a scientific or medical publication:

(1) That is published by an organization that has an editorial board, that uses experts who have demonstrated expertise in the subject of an article under review by the organization and who are independent of the organization, to review and objectively select, reject, or provide comments about proposed articles, and that has a publicly stated policy, to which the organization adheres,

of full disclosure of any conflict of interest or biases for all authors or contributors involved with the journal or organization;

(2) Whose articles are peer-reviewed and published in accordance with the regular peer-review procedures of the organization;

(3) That is generally recognized to be of national scope and reputation;

(4) That is indexed in the Index Medicus of the National Library of Medicine of the National Institutes of Health; and

(5) That is not in the form of a special supplement that has been funded in whole or in part by one or more manufacturers.

(k) *Supplemental application* means:

(1) For drugs, a supplement to support a new use to an approved new drug application;

(2) For biologics, a supplement to an approved license application;

(3) For devices that are the subject of a cleared 510(k) submission and devices that are exempt from the 510(k) process, a new 510(k) submission to support a new use or, for devices that are the subject of an approved premarket approval application, a supplement to support a new use to an approved premarket approval application.

Subpart B—Information To Be Disseminated

§ 99.101 Information that may be disseminated.

(a) A manufacturer may disseminate written information concerning the safety, effectiveness, or benefit of a use not described in the approved labeling for an approved drug or device or in the statement of intended use for a cleared device, provided that the manufacturer complies with all other relevant requirements under this part. Such information shall:

(1) Be about a drug or device that has been approved, licensed, or cleared for marketing by FDA;

(2) Be in the form of:

(i) An unabridged reprint or copy of an article, peer-reviewed by experts qualified by scientific training or experience to evaluate the safety or effectiveness of the drug or device involved, which was published in a scientific or medical journal. In addition, the article must be about a clinical investigation with respect to the drug or device and must be considered to be scientifically sound by the experts described in this paragraph; or

(ii) An unabridged reference publication that includes information about a clinical investigation with respect to the drug or device, which experts qualified by scientific training or experience to evaluate the safety or effectiveness of the drug or device that is the subject of the clinical investigation would consider to be scientifically sound;

(3) Not pose a significant risk to the public health;

(4) Not be false or misleading. FDA may consider information disseminated under this part to be false or misleading if, among other things, the information includes only favorable publications when unfavorable publications exist or excludes articles, reference publications, or other information required under § 99.103(a)(4) or the information presents conclusions that clearly cannot be supported by the results of the study; and

(5) Not be derived from clinical research conducted by another manufacturer unless the manufacturer disseminating the information has the permission of such other manufacturer to make the dissemination.

(b) For purposes of this part:

(1) FDA will find that all journal articles and reference publications (as those terms are defined in § 99.3) are scientifically sound except:

(i) Letters to the editor;

(ii) Abstracts of a publication;

(iii) Those regarding Phase 1 trials in healthy people;

(iv) Flagged reference publications that contain little or no substantive discussion of the relevant clinical investigation; and

(v) Those regarding observations in four or fewer people that do not reflect any systematic attempt to collect data, unless the manufacturer demonstrates to FDA that such reports could help guide a physician in his/her medical practice.

(2) A reprint or copy of an article or reference publication is ''unabridged'' only if it retains the same appearance, form, format, content, or configuration as the original article or publication. Such reprint, copy of an article, or reference publication shall not be disseminated with any information that is promotional in nature. A manufacturer may cite a particular discussion about a new use in a reference publication in the explanatory or other information attached to or otherwise accompanying the reference publication under § 99.103.

§ 99.103 Mandatory statements and information.

(a) Any information disseminated under this part shall include:

(1) A prominently displayed statement disclosing:

(i) For a drug, ''This information concerns a use that has not been approved by the Food and Drug Administration.'' For devices, the statement shall read, ''This information concerns a use that has not been approved or cleared by the Food and Drug Administration.'' If the information to be disseminated includes both an approved and unapproved use or uses or a cleared and uncleared use or uses, the manufacturer shall modify the statement to identify the unapproved or uncleared new use or uses. The manufacturer shall permanently affix the statement to the front of each reprint or copy of an article from a scientific or medical journal and to the front of each reference publication disseminated under this part;

(ii) If applicable, the information is being disseminated at the expense of the manufacturer;

(iii) If applicable, the names of any authors of the information who were employees of, or consultants to, or received compensation from the manufacturer, or who had a significant financial interest in the manufacturer during the time that the study that is the subject of the dissemination was conducted up through 1 year after the time the article/reference publication was written and published;

(iv) If applicable, a statement that there are products or treatments that have been approved or cleared for the use that is the subject of the information being disseminated; and

(v) The identification of any person that has provided funding for the conduct of a study relating to the new use of a drug or device for which such information is being disseminated; and

(2) The official labeling for the drug or device;

(3) A bibliography of other articles (that concern reports of clinical investigations both supporting and not supporting the new use) from a scientific reference publication or scientific or medical journal that have been previously published about the new use of the drug or device covered by the information that is being disseminated, unless the disseminated information already includes such a bibliography; and

(4) Any additional information required by FDA under § 99.301(a)(2). Such information shall be attached to the front of the disseminated information or, if attached to the back of the disseminated information, its presence shall be made known to the reader by a sticker or notation on the front of the disseminated information and may consist of:

(i) Objective and scientifically sound information pertaining to the safety or effectiveness of the new use of the drug or device and which FDA determines is necessary to provide objectivity and balance. This may include information that the manufacturer has submitted to FDA or, where appropriate, a summary of such information and any other information that can be made publicly available; and

(ii) An objective statement prepared by FDA, based on data or other scientifically sound information, bearing on the safety or effectiveness of the new use of the drug or device.

(b) Except as provided in paragraphs (a)(1)(i) and (a)(4) of this section, the statements, bibliography, and other information required by this section shall be attached to such disseminated information.

(c) For purposes of this section, factors to be considered in determining whether a statement is ''prominently displayed'' may include, but are not limited to, type size, font, layout, contrast,

graphic design, headlines, spacing, and any other technique to achieve emphasis or notice. The required statements shall be outlined, boxed, highlighted, or otherwise graphically designed and presented in a manner that achieves emphasis or notice and is distinct from the other information being disseminated.

§ 99.105 Recipients of information.

A manufacturer disseminating information on a new use under this part may only disseminate that information to a health care practitioner, a pharmacy benefit manager, a health insurance issuer, a group health plan, or a Federal or State Government agency.

Subpart C—Manufacturer's Submissions, Requests, and Applications

§ 99.201 Manufacturer's submission to the agency.

(a) Sixty days before disseminating any written information concerning the safety, effectiveness, or benefit of a new use for a drug or device, a manufacturer shall submit to the agency:

(1) An identical copy of the information to be disseminated, including any information (e.g., the bibliography) and statements required under § 99.103;

(2) Any other clinical trial information which the manufacturer has relating to the effectiveness of the new use, any other clinical trial information that the manufacturer has relating to the safety of the new use, any reports of clinical experience pertinent to the safety of the new use, and a summary of such information. For purposes of this part, clinical trial information includes, but is not limited to, published papers and abstracts, even if not intended for dissemination, and unpublished manuscripts, abstracts, and data analyses from completed or ongoing investigations. The reports of clinical experience required under this paragraph shall include case studies, retrospective reviews, epidemiological studies, adverse event reports, and any other material concerning adverse effects or risks reported for or associated with the new use. If the manufacturer has no knowledge of clinical trial information relating to the safety or effectiveness of the new

use or reports of clinical experience pertaining to the safety of the new use, the manufacturer shall provide a statement to that effect;

(3) An explanation of the manufacturer's method of selecting the articles for the bibliography (e.g., the databases or sources and criteria (i.e., subject headings/keywords) used to generate the bibliography and the time period covered by the bibliography); and

(4) If the manufacturer has not submitted a supplemental application for the new use, one of the following:

(i) If the manufacturer has completed studies needed for the submission of a supplemental application for the new use:

(A) A copy of the protocol for each completed study or, if such protocol was submitted to an investigational new drug application or an investigational device exemption, the number(s) for the investigational new drug application or investigational device exemption covering the new use, the date of submission of the protocol(s), the protocol number(s), and the date of any amendments to the protocol(s); and

(B) A certification stating that, ''On behalf of [insert manufacturer's name], I certify that [insert manufacturer's name] has completed the studies needed for the submission of a supplemental application for [insert new use] and will submit a supplemental application for such new use to the Food and Drug Administration no later than [insert date no later than 6 months from date that dissemination of information under this part can begin]''; or

(ii) If the manufacturer has planned studies that will be needed for the submission of a supplemental application for the new use:

(A) The proposed protocols and schedule for conducting the studies needed for the submission of a supplemental application for the new use. The protocols shall comply with all applicable requirements in parts 312 of this chapter (investigational new drug applications) and 812 of this chapter (investigational device exemptions). The schedule shall include the projected dates on which the manufacturer expects the principal study events to occur (e.g., initiation and completion of

patient enrollment, completion of data collection, completion of data analysis, and submission of the supplemental application); and

(B) A certification stating that, ''On behalf of [insert manufacturer's name], I certify that [insert manufacturer's name] will exercise due diligence to complete the clinical studies necessary to submit a supplemental application for [insert new use] and will submit a supplemental application for such new use to the Food and Drug Administration no later than [insert date no later than 36 months from date that dissemination of information under this part can begin or no later than such time period as FDA may specify pursuant to an extension granted under § 99.303(a)];'' or

(iii) An application for exemption from the requirement of a supplemental application; or

(5) If the manufacturer has submitted a supplemental application for the new use, a cross-reference to that supplemental application.

(b) The manufacturer's attorney, agent, or other authorized official shall sign the submission and certification statement or application for exemption. If the manufacturer does not have a place of business in the United States, the submission and certification statement or application for exemption shall contain the signature, name, and address of the manufacturer's attorney, agent, or other authorized official who resides or maintains a place of business in the United States.

(c) The manufacturer shall send three copies of the submission and certification statement or application for exemption to FDA. The outside of the shipping container shall be marked as ''Submission for the Dissemination of Information on an Unapproved/New Use.'' The manufacturer shall send the submission and certification statement or application for exemption to the appropriate FDA component listed in paragraphs (c)(1) through (c)(3) of this section.

(1) For biological products and devices regulated by the Center for Biologics Evaluation and Research, the Advertising and Promotional Labeling Staff (HFM–602), Center for Biologics Evaluation and Research, Food and Drug Administration, 1401 Rockville Pike, Rockville, MD 20852;

(2) For human drug products, the Division of Drug Marketing, Advertising, and Communications (HFD–40), Center for Drug Evaluation and Research, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857; or

(3) For medical devices, the Promotion and Advertising Policy Staff (HFZ–302), Office of Compliance, Center for Devices and Radiological Health, Food and Drug Administration, 2098 Gaither Rd., Rockville, MD 20850.

(d) The 60-day period shall begin when FDA receives a manufacturer's submission, including, where applicable, a certification statement or an application for an exemption.

§ 99.203 Request to extend the time for completing planned studies.

(a) A manufacturer may request, prior to or at the time of making a submission to FDA under § 99.201, that FDA extend the 36-month time period for completing the studies and submitting a supplemental application for the new use that is the subject of the information to be disseminated. Such request must set forth the reasons that such studies cannot be completed and submitted in a supplemental application within 36 months.

(b) A manufacturer who has certified that it will complete the studies necessary to submit a supplemental application for a new use within a specified period of time from the date that dissemination of information under this part can begin under § 99.201(a)(4)(ii), but later finds that it will be unable to complete such studies and submit a supplemental application within that time period may request an extension of time from FDA. The manufacturer, in its request for extension, shall identify the product, the new use, and shall:

(1) Describe the study or studies that cannot be completed on time and explain why the study or studies cannot be completed on time;

(2) Describe the current status of the incomplete study or studies and summarize the work conducted, including the dates on which principal events concerning the study or studies occurred; and

(3) Estimate the additional time needed to complete the studies and submit a supplemental application. The requested extension shall not exceed an additional 24 months.

(c) The manufacturer shall send three copies of the request for extension to the same FDA office that received the manufacturer's initial submission and certification statement. The outside of the envelope shall be marked as ''Request for Time Extension—Dissemination of Information on an Unapproved Use.''

§ 99.205 Application for exemption from the requirement to file a supplemental application.

(a) In certain circumstances, described in paragraph (b) of this section, a manufacturer may submit an application for an exemption from the requirement to submit a supplemental application for a new use for purposes of disseminating information on that use.

(b) The manufacturer's application for an exemption shall identify the basis for the proposed exemption and shall include materials demonstrating that it would be economically prohibitive or that it would be unethical to conduct the studies necessary to submit a supplemental application for the new use.

(1) If the basis for the manufacturer's application for exemption is that it would be economically prohibitive to incur the costs necessary to submit a supplemental application for a new use, the manufacturer shall, at a minimum, provide:

(i) Evidence explaining why existing data characterizing the safety and effectiveness of the drug or device, including data from the study described in the information to be disseminated, are not adequate to support the submission of a supplemental application for the new use. Such evidence shall include an analysis of all data relevant to the safety and effectiveness of the use, a summary of those data, and any documentation resulting from prior discussions with the agency concerning the adequacy of the existing data; and

(ii) Evidence demonstrating that the cost of the study or studies for the new use reasonably exceeds the expected revenue from the new use minus the costs of goods sold and marketing and administrative expenses attributable to the new use of the product. Such evidence shall include:

(A) A description of the additional studies that the manufacturer believes are necessary to support the submission of a supplemental application for the new use, including documentation from prior discussions, if any, with the agency concerning the studies that would be needed, and an estimate of the projected costs for such studies;

(B) The expected patient population for the new use;

(C) The expected revenue for the new use, including an explanation of the price at which the drug or device will be sold;

(D) Any exclusivity for the drug or device for the new use; and

(E) Any other information that the manufacturer has showing that conducting the studies on the new use would be economically prohibitive; and

(iii) An attestation by a responsible individual of the manufacturer or an individual acting on the manufacturer's behalf verifying that the estimates included with the submission are accurate and were prepared in accordance with generally accepted accounting procedures. The data underlying and supporting the estimates shall be made available to FDA upon request. Alternatively, a manufacturer may submit a report of an independent certified public accountant in accordance with the Statement of Standards for Attestation established by the American Institute of Certified Public Accountants and agreed upon procedures performed with respect to the estimates submitted under this section.

(2) If the basis for the manufacturer's application for exemption is that it would be unethical to conduct the studies necessary for the supplemental application for a new use, the manufacturer shall provide evidence:

(i) Explaining why existing data characterizing the safety and effectiveness of the drug or device, including data from the study described in the information to be disseminated, are not adequate to support the submission of a supplemental application for the new use. Such evidence

shall include an analysis of all data relevant to the safety and effectiveness of the new use, a summary of those data, and any documentation resulting from prior discussions with the agency concerning the adequacy of the existing data; and

(ii) Explaining why it would be unethical to conduct the further studies that would be necessary for the approval of the new use. Such evidence shall establish that, notwithstanding the insufficiency of available data to support the submission of a supplemental application for the new use, the data are persuasive to the extent that withholding the drug or device in a controlled study (e.g., by providing no therapy, a placebo, an alternative therapy, or an alternative dose) would pose an unreasonable risk of harm to human subjects. In assessing the appropriateness of conducting studies to support the new use, the manufacturer may provide evidence showing that the new use is broadly accepted as current standard medical treatment or therapy. The manufacturer shall also address the possibility of conducting studies in different populations or of modified design (e.g., adding the new therapy to existing treatments or using an alternative dose if monotherapy studies could not be conducted).

Subpart D—FDA Action on Submissions, Requests, and Applications

§ 99.301 Agency action on a submission.

(a) *Submissions.* Within 60 days after receiving a submission under this part, FDA may:

(1) Determine that the manufacturer does not comply with the requirements under this part and that, as a result, the manufacturer shall not disseminate any information under this part;

(2) After providing the manufacturer notice and an opportunity for a meeting, determine that the information submitted regarding a new use fails to provide data, analyses, or other written matter that is objective and balanced and:

(i) Require the manufacturer to disseminate additional information, including information that the manufacturer has submitted to FDA or, where appropriate, a summary of such information or any other information that can be made publicly available, which, in the agency's opinion:

(A) Is objective and scientifically sound;

(B) Pertains to the safety or effectiveness of the new use; and

(C) Is necessary to provide objectivity and balance; and

(ii) Require the manufacturer to disseminate an objective statement prepared by FDA that is based on data or other scientifically sound information available to the agency and bears on the safety or effectiveness of the drug or device for the new use; and

(3) Require the manufacturer to maintain records that will identify individual recipients of the information that is to be disseminated when such individual records are warranted due to special safety considerations associated with the new use.

(b) *Protocols/Studies*. Within 60 days after receiving a submission under this part, FDA shall:

(1) If the manufacturer has planned studies that will be needed for the submission of a supplemental application for the new use, review the manufacturer's proposed protocols and schedule for completing such studies and determine whether the proposed protocols are adequate and whether the proposed schedule for completing the studies is reasonable. FDA shall notify the manufacturer of its determination; or

(2) If the manufacturer has completed studies that the manufacturer believes would be an adequate basis for the submission of a supplemental application for the new use, conduct a review of the protocols submitted for such studies to determine whether they are adequate. FDA shall notify the manufacturer of its determination.

§ 99.303 Extension of time for completing planned studies.

(a) Upon review of a drug or device manufacturer's proposed protocols and schedules for conducting studies needed for the submission of a supplemental application for a new use, FDA may, with or without a request for an extension from the manufacturer, determine that such studies cannot be completed and submitted within 36 months. The agency may exercise its discretion in extending the time period for completing the studies and submitting a supplemental application. Extensions under this paragraph are not subject to any time limit, but shall be made before the

manufacturer begins the studies needed for the submission of a supplemental application for the new use.

(b) The manufacturer may, after beginning the studies needed for the submission of a supplemental application for a new use, request in writing that FDA extend the time period for conducting studies needed for the submission of a supplemental application for a new use and submitting a supplemental application to FDA. FDA may grant or deny the request or, after consulting the manufacturer, grant an extension different from that requested by the manufacturer. FDA may grant a manufacturer's request for an extension if FDA determines that the manufacturer has acted with due diligence to conduct the studies needed for the submission of a supplemental application for a new use and to submit such a supplemental application to FDA in a timely manner and that, despite such actions, the manufacturer needs additional time to complete the studies and submit the supplemental application. Extensions under this paragraph shall not exceed 24 months.

(c) If FDA extends the time period for completing the studies and submitting a supplemental application under paragraph (a) of this section after the manufacturer has submitted a certification under § 99.201(a)(4)(ii)(B), or if FDA grants a manufacturer's request for an extension under paragraph (b) of this section, the manufacturer shall submit a new certification under § 99.201(a)(4)(ii)(B) that sets forth the timeframe within which clinical studies will be completed and a supplemental application will be submitted to FDA.

§ 99.305 Exemption from the requirement to file a supplemental application.

(a) Within 60 days after receipt of an application for an exemption from the requirement of a supplemental application, FDA shall approve or deny the application.

(1) If FDA does not act on the application for an exemption within the 60-day period, the application for an exemption shall be deemed to be approved.

(2) If an application for an exemption is deemed to be approved, FDA may, at any time, terminate such approval if it determines that the requirements for granting an exemption have not been met. FDA shall notify the manufacturer if the approval is terminated.

(b) In reviewing an application for an exemption, FDA shall consider the materials submitted by the manufacturer and may consider any other appropriate information, including, but not limited to, any pending or previously approved applications for exemption submitted by the manufacturer.

(c) FDA may grant an application for an exemption if FDA determines that:

(1) It would be economically prohibitive for the manufacturer to incur the costs necessary to submit a supplemental application for a new use, which at a minimum requires:

(i) That existing data characterizing the safety and effectiveness of the drug or device, including data from the study described in the information to be disseminated are not adequate to support the submission of a supplemental application for the new use; and

(ii) That the cost of the study or studies for the new use reasonably exceeds the expected revenue from the new use minus the cost of goods sold and marketing and administrative expenses attributable to the new use of the product, and there are not less expensive ways to obtain the needed information; or

(2) It would be unethical to conduct clinical studies needed to support the submission of a supplemental application for the new use because:

(i) Existing data characterizing the safety and effectiveness of the drug or device, including data from the study described in the information to be disseminated are not adequate to support the submission of a supplemental application for the new use; and

(ii) Although available evidence would not support the submission of a supplemental application for the new use, the data are persuasive to the extent that withholding the drug or device in a controlled study would pose an unreasonable risk of harm to human subjects and no studies in different populations or of modified design can be utilized. In determining whether it would be unethical to conduct clinical studies, the agency shall consider, in addition to the persuasiveness of available evidence of effectiveness, whether the new use of the drug or device is broadly accepted as current standard medical treatment or therapy.

Subpart E—Corrective Actions and Cessation of Dissemination

§ 99.401 Corrective actions and cessation of dissemination of information.

(a) *FDA actions based on post dissemination data.* If FDA receives data after a manufacturer has begun disseminating information on a new use and, based on that data, determines that the new use that is the subject of information disseminated under this part may not be effective or may present a significant risk to public health, FDA shall consult the manufacturer and, after such consultation, take appropriate action to protect the public health. Such action may include ordering the manufacturer to cease disseminating information on the new use and to take appropriate corrective action.

(b) *FDA actions based on information disseminated by a manufacturer.* If FDA determines that a manufacturer is disseminating information that does not comply with the requirements under this part, FDA may:

(1) Provide to the manufacturer an opportunity to bring itself into compliance with the requirements under this part if the manufacturer's noncompliance constitutes a minor violation of these requirements; or

(2) Order the manufacturer to cease dissemination of information and to take corrective action. FDA shall issue such an order only after it has:

(i) Provided notice to the manufacturer regarding FDA's intent to issue an order to cease dissemination; and

(ii) Provided to the manufacturer an opportunity for a meeting. FDA need not provide an opportunity for a meeting if the manufacturer certified that it will submit a supplemental application for the new use within 6 months of the date that dissemination can begin and the noncompliance involves a failure to submit such supplemental application.

(c) *FDA actions based on a manufacturer's supplemental application.* FDA may order a manufacturer to cease disseminating information under this part and to take corrective action if:

(1) In the case of a manufacturer that has submitted a supplemental application for the new use, FDA determines that the supplemental application does not contain adequate information for approval of the new use;

(2) In the case of a manufacturer that has certified that it will submit a supplemental application for the new use within 6 months, the manufacturer has not, within the 6-month period, submitted a supplemental application for the new use;

(3) In the case of a manufacturer that has certified that it will submit a supplemental application for the new use within 36 months or within such time as FDA has determined to be appropriate under § 99.303(a) or (b), such manufacturer has not submitted the supplemental application within the certified time, or FDA, after an informal hearing, has determined that the manufacturer is not acting with due diligence to initiate or complete the studies necessary to support a supplemental application for the new use; or

(4) In the case of a manufacturer that has certified that it will submit a supplemental application for the new use within 36 months or within such time as FDA has determined to be appropriate under § 99.303(a) or (b), the manufacturer has discontinued or terminated the clinical studies that would be necessary to support a supplemental application for a new use.

(d) *Effective date of orders to cease dissemination.* An order to cease dissemination of information shall be effective upon date of receipt by the manufacturer, unless otherwise stated in such order.

(e) *Cessation of dissemination by a noncomplying manufacturer.* A manufacturer that begins to disseminate information in compliance with this part, but subsequently fails to comply with this part, shall immediately cease disseminating information under this part. A manufacturer that discontinues, terminates, or fails to conduct with due diligence clinical studies that it certified it would complete under § 99.201(a)(4)(ii) shall be deemed not in compliance with this part. A manufacturer shall notify FDA immediately if it ceases dissemination under this paragraph.

§ 99.403 Termination of approvals of applications for exemption.

(a) FDA may, at any time, terminate the approval of an application for an exemption from the requirement to file a supplemental application if:

(1) The application for an exemption had been deemed to be approved because the agency had not acted on the application within 60 days after its receipt by FDA;

(2) The manufacturer is disseminating written information on the new use; and

(3) FDA determines that it would be economically and ethically possible for the manufacturer to conduct the clinical studies needed to submit a supplemental application for the new use.

(b) If FDA terminates a deemed approval of an application for an exemption under paragraph (a) of this section, FDA also may:

(1) Order the manufacturer to cease disseminating information; and

(2) Order the manufacturer to take action to correct the information that has been disseminated if FDA determines that the new use described in the disseminated information would pose a significant risk to public health.

(c) FDA shall notify the manufacturer if it terminates the deemed approval of an application for an exemption under paragraph (a) of this section. If FDA also issues an order to cease dissemination of information, the manufacturer shall comply with the order no later than 60 days after its receipt.

(d) FDA may, at any time, terminate the approval of an application for an exemption from the requirement to file a supplemental application for a new use if, after consulting with the manufacturer that was granted such exemption, FDA determines that the manufacturer no longer meets the requirements for an exemption on the basis that it is economically prohibitive or unethical to conduct the studies needed to submit a supplemental application for the new use.

(e) If FDA terminates an approval of an application for an exemption under paragraph (d) of this section, the manufacturer must, within 60 days of being notified by FDA that its exemption approval has been terminated, file a supplemental application for the new use that is the subject of the information being disseminated under the exemption, certify, under § 99.201(a)(4)(i) or

(a)(4)(ii) that it will file a supplemental application for the new use, or cease disseminating the information on the new use. FDA may require a manufacturer that ceases dissemination of information on the new use to undertake corrective action.

§ 99.405 Applicability of labeling, adulteration, and misbranding authority.

The dissemination of information relating to a new use for a drug or device may constitute labeling, evidence of a new intended use, adulteration, or misbranding of the drug or device if such dissemination fails to comply with section 551 of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 360aaa) and the requirements of this part. A manufacturer's failure to exercise due diligence in submitting the clinical studies that are necessary for the approval of a new use that is the subject of information disseminated under this part or in beginning or completing such clinical studies shall be deemed a failure to comply with section 551 of the act and the requirements of this part.

Subpart F—Recordkeeping and Reports

§ 99.501 Recordkeeping and reports.

(a) A manufacturer disseminating information under this part shall:

(1) Maintain records sufficient to allow the manufacturer to take corrective action as required by FDA. The manufacturer shall make such records available to FDA, upon request, for inspection and copying. Such records shall either:

(i) Identify, by name, those persons receiving the disseminated information; or

(ii) Identify, by category, the recipients of the disseminated information, unless FDA requires the manufacturer to retain records identifying individual recipients of the disseminated information. Manufacturers whose records identify recipients by category only shall:

(A) Identify subcategories of recipients where appropriate (e.g., oncologists, pediatricians, obstetricians, etc.); and

(B) Ensure that any corrective action to be taken will be sufficiently conspicuous to individuals within that category of recipients;

(2) Maintain an identical copy of the information disseminated under this part; and

(3) Upon the submission of a supplemental application to FDA, notify the appropriate office identified in § 99.201(c) of this part.

(b) A manufacturer disseminating information on a new use for a drug or device shall, on a semiannual basis, submit to the FDA office identified in § 99.201(c) of this part:

(1) A list containing the titles of articles and reference publications relating to the new use of drugs or devices that the manufacturer disseminated to a health care practitioner, pharmacy benefit manager, health insurance issuer, group health plan, or Federal or State Government agency. The list shall cover articles and reference publications disseminated in the 6-month period preceding the date on which the manufacturer provides the list to FDA;

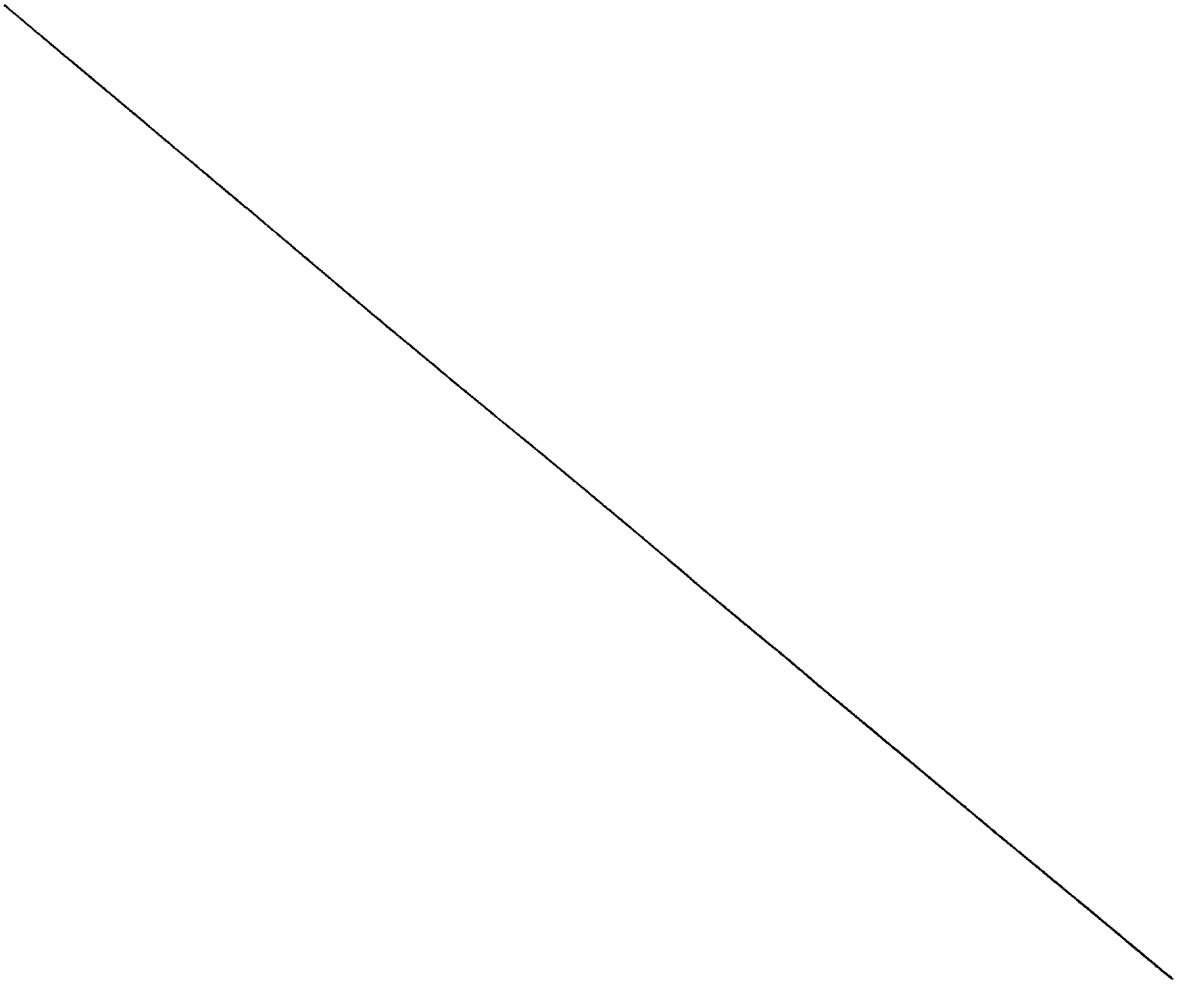
(2) A list identifying the categories of health care practitioners, pharmacy benefit managers, health insurance issuers, group health plans, or Federal or State Government agencies that received the articles and reference publications in the 6-month period described in paragraph (b)(1) of this section. The list shall also identify which category of recipients received a particular article or reference publication;

(3) A notice and summary of any additional clinical research or other data relating to the safety or effectiveness of the new use, and, if the manufacturer possesses such clinical research or other data, a copy of the research or data. Such other data may include, but is not limited to, new articles published in scientific or medical journals, reference publications, and summaries of adverse effects that are or may be associated with the new use;

(4) If the manufacturer is conducting studies necessary for the submission of a supplemental application, the manufacturer shall submit periodic progress reports on these studies to FDA. Such reports shall describe the studies' current status (i.e., progress on patient enrollment, any significant problems that could affect the manufacturer's ability to complete the studies, and expected

completion dates). If the manufacturer discontinues or terminates a study before completing it, the manufacturer shall, as part of the next periodic progress report, state the reasons for such discontinuation or termination; and

(5) If the manufacturer was granted an exemption from the requirements to submit a supplemental application for the new use, any new or additional information that relates to whether the manufacturer continues to meet the requirements for such exemption. This information may include, but is not limited to, new or additional information regarding revenues from the product that is the subject of the dissemination and new or additional information regarding the persuasiveness of the data on the new use, including information regarding whether the new use is broadly accepted as current standard medical treatment or therapy.



(c) A manufacturer shall maintain a copy of all information, lists, records, and reports required

(c) A manufacturer shall maintain a copy of all information, lists, records, and reports required or disseminated under this part for 3 years after it has ceased dissemination of such information and make such documents available to FDA for inspection and copying.

Dated: NOV 17 1998

Michael A. Friedman,

Acting Commissioner for Food and Drugs.

Donna E. Shalala,

Secretary of Health and Human Services.

[FR Doc. 98–???? Filed ??–??–98; 8:45 am]

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